ABSORB GT1™ BIORESORBABLE VASCULAR SCAFFOLD SYSTEM

SPONSOR EXECUTIVE SUMMARY FOR THE CIRCULATORY SYSTEMS DEVICE PANEL ADVISORY COMMITTEE

MEETING DATE: 15 March 2016

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Table of Acronyms

Ach	Acetylcholine
ACS	Acute coronary syndromes
AMI	Acute myocardial infarction
ARC	Academic Research Consortium
AT	As treated
atm	Atmosphere
AUC_{last}	Area under the curve
BMS	Bare metal stents
BVS	Bioresorbable vascular scaffold
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CD	Cardiac death
CEC	Clinical Events Committee
CI	Confidence interval
CK	Creatine kinase
CK-MB	Creatine kinase-MB
C_{max}	Maximal whole blood concentration
CSS	Coronary stent system
DAPT	Dual anti-platelet therapy
DES	Drug-eluting stents
DM	Diabetes mellitus
DMR	All death, all mi (regardless of MI definition), all revascularization
DS	Diameter stenosis
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
GFR	Glomerular filtration rate
GLP	Good laboratory practice
ID-TLR	Ischemia-driven target lesion revascularization
ID-TVR	Ischemia-driven target vessel revascularization
ITT	Intent-to-treat
IVUS	Intravascular ultrasound
LAD	Left anterior descending artery
LCX	Left circumflex artery
LMCA	Left main coronary artery
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular event
MSCT	Multislice computed tomography
MUGA	Multiple-Gated Acquisition
MI	Myocardial infarction

MRI	Magnetic resonance imaging
NHLBI	National Heart, Lung, and Blood Institute
NTG	Nitroglycerin
NQ-MI	Non-Q-wave myocardial infarction
NSTEMI	Non-ST segment myocardial infarction
OCT	Optical coherence tomography
ODS	Optimized delivery system
OUS	Outside the U.S.
PK	Pharmacokinetic
pKa	Acid dissociation constant
PLA	Poly lactic acid / poly lactide
PLLA	Poly(L-lactide)
PDLLA	Poly(D,L-lactide)
PCI	Percutaneous coronary intervention
PG	Performance goal
POBA	Plain old balloon angioplasty
PTCA	Percutaneous transluminal coronary angioplasty
PTE	Per-treatment-evaluable
PVA	Poly(vinyl alcohol)
QCA	Quantitative coronary analysis
Q-MI	Q-Wave myocardial infarction
RCA	Right coronary artery
RCT	Randomized controlled trial
RVD	Reference vessel diameter
RX	Rapid exchange
SEM	Scanning electron microscopy
ST	Stent / scaffold thrombosis
STEMI	ST segment myocardial infarction
TLF	Target lesion failure
TLR	target lesion revascularization
TIMI	Thrombosis in Myocardial Infarction
$T_{1/2}$	Terminal elimination half-life
T_{max}	Time to reach the maximal whole blood concentration
TV-MI	Target vessel myocardial infarction
TVR	Target vessel revascularization
ULN	Upper limit of normal
ZES	Zotorolimus eluting stent

1.0 Sponsor Executive Summary Overview

Key Points:

- The Absorb GT1™ Bioresorbable Vascular Scaffold (BVS) System (Absorb) is a first of its kind fully bioresorbable percutaneous coronary intervention (PCI) technology. Absorb functions like a drug eluting stent (DES) in the first year, gradually resorbing over time leaving the vessel free of a permanent implant and able to heal to a more normal physiological state.
- The ABSORB III randomized clinical trial was conducted to establish a reasonable assurance of safety and effectiveness of Absorb in the first year. The ABSORB III trial met the primary endpoint of non-inferiority of Absorb compared to the control Xience, in target lesion failure (TLF) at 1 year. There were no statistical differences between Absorb and Xience for safety or effectiveness.
- Absorb is effective as demonstrated by preserving the treatment effect of DES over bare metal stents by reducing the need for repeat revascularization.
- Absorb safety is confirmed, and particularly when examining the outcomes in the intended patient population aligned with the label (2.5-3.75 mm).
- Long-term data from earlier trials with Absorb provides supporting information that after 1 year, Absorb accrues either similar or less TLF/MACE rates compared to XIENCE.
- In summary, the ABSORB III trial, by showing comparable safety and effectiveness rates to Xience, demonstrates that the benefits of Absorb outweigh the risks, offering patients the option of having a PCI procedure that performs similar to a DES but without a permanent implant.

1.1 Introduction

The Absorb GT1 Bioresorbable Vascular Scaffold (BVS) System (Absorb) is a first of its kind fully bioresorbable PCI technology. As Absorb was designed to perform like a DES in the first year, the pivotal ABSORB III trial was established to evaluate Absorb using current Food and Drug Administration (FDA) regulatory guidance for the approval of coronary DES [1]. This includes:

1) a non-inferiority design to demonstrate Absorb is non-inferior to FDA approved DES,

2) the use of the FDA-recommended device oriented composite endpoint, target lesion failure (cardiac death, target vessel MI and ischemic driven target lesion revascularization) as the primary outcome measure to evaluate a combination of safety and effectiveness at 1 year, and

3) the selection of a non-inferiority margin for statistical analysis based on current FDA guidance on non-inferiority clinical trials [2].

Therefore, the evaluation of safety and effectiveness of Absorb follows the same regulatory standard of all second generation DES that have been approved by the FDA.

In addition, Absorb being a bioresorbable technology offers practical benefits that could address limitations of metallic stents such as:

- "full metal jacket" (vessel lined up with metal stents in patients with long disease) (see **Figure 2.0-3** in **Section 2.0**),
- permanent jailed side branches (refer to **Figure 6.4.2-2** in **Section 6.4.2**),
- re-narrowing of the vessel when treating in-stent restenosis with a second metallic stent, and
- blooming artifact in multislice computed tomography (MSCT) hindering analysis (refer to **Figure 6.5-1** in **Section 6.5**).

The ABSORB III trial was conducted to establish that the safety and effectiveness of Absorb is similar to a best-in-class DES, Xience, in the first year. Approval of Absorb based on the 1 year data provides the necessary foundation that opens the door for future demonstration of the long term benefits of a fully resorbable implant. The long term benefits of Absorb are under evaluation in the currently enrolling ABSORB IV trial, which is designed to demonstrate superiority to Xience in the primary endpoint of target lesion failure between 1 and 5 years. As such, ABSORB IV is not part of this regulatory assessment for initial U.S. approval.

1.2 Product Overview

Absorb is a first of its kind fully bioresorbable drug eluting scaffold for use in the coronary vasculature. The bioresorbable polymer poly(L-lactide) (PLLA) scaffold is coated with a blend of the antiproliferative drug everolimus and bioresorbable polymer poly(D,L-lactide) (PDLLA) and pre-mounted on a rapid exchange (RX) scaffold delivery system. It is comprised of a series of circumferentially-oriented sinusoidal rings that open during expansion. Two platinum markers are embedded at each end to enable fluoroscopic visualization as the scaffold material is not radiopaque.

The ABSORB III Randomized Controlled Trial (RCT) conducted to support US approval utilized the Absorb™ Bioresorbable Vascular Scaffold (BVS) System. Abbott Vascular is seeking FDA approval of the Absorb GT1 BVS System. The only difference between the Absorb BVS System used in the clinical trial and the Absorb GT1 BVS System is the delivery system chassis which was slightly modified to improve deliverability. The implanted device (scaffold, drug coating, drug dose density and platinum marker beads) and the delivery system balloon are the same for both systems; therefore, the clinical results from the ABSORB III RCT trial are directly applicable to the Absorb GT1 BVS System.

Abbott Vascular is pursuing approval of the Absorb GT1 BVS System in the United States under PMA P150023. Abbott Vascular proposes the following indication for the Absorb GT1 BVS System:

> The Absorb GT1 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.

Further details about Absorb can be found in **Section 4.0**. Within this document, all references to Absorb or Absorb BVS System are synonymous and directly applicable to the Absorb GT1 BVS System.

1.2.1 Principle of Operation

The performance of Absorb is designed to evolve over time after implantation, and can be described by three phases of functionality, namely *revascularization*, *restoration*, and *resorption*. Each phase is described below.

Revascularization: In the revascularization phase (from implantation to 6 months), Absorb is intended to perform similarly to a metallic DES, by releasing everolimus at a rate that inhibits smooth muscle cell proliferation while allowing for endothelialization and the controlled formation of neointima. To maintain lumen patency, Absorb is designed to provide mechanical support for a minimum of 3 months to allow the vessel to stabilize following implantation. Structural integrity of the scaffold is designed to be maintained at least through 6 months after implantation to ensure neointimal coverage of the scaffold struts prior to the eventual loss of continuity.

Restoration: The restoration phase (from 6 to approximately 18 months after implantation) represents the transition of Absorb from a vehicle for drug delivery and vessel support to a passive implant. As degradation continues through this phase, the scaffold transitions to a discontinuous structure, and ceases to constrain the vessel. As the struts are covered by neointima by 6 months, the continuing scaffold degradation does not pose an embolic risk.

Resorption: By the beginning of the resorption phase (approximately 18 months after implantation), Absorb has lost structural integrity (support and continuity) and is a

functionally inert implant. As described in **Section 4.5.2**, during this phase the benign resorption of PLA continues, with complete resorption occurring by approximately 36 months.

1.2.2 Preclinical Evidence

Extensive preclinical evaluation has been conducted to evaluate the safety of Absorb through each of these performance phases, with follow-ups from 3 days through 48 months. These studies have demonstrated the acute and long term safety of Absorb, including specifically rapid coverage of struts with endothelialized neointima; low inflammation, including during the period of most active degradation; complete integration of struts into the arterial wall; and a lack of scaffold thrombosis or distal embolization as based on the evaluation of downstream myocardium and peripheral organs.

1.3 Pivotal US Clinical Trial: ABSORB III Randomized Controlled Trial

Key Points:

- ABSORB III achieved its primary study objective, demonstrating non-inferiority in TLF at 1 year compared to Xience in the ITT population (**Table 1.3.2-1**). The design and results of the ABSORB III trial meet FDA's regulatory standard for approval of coronary DES.
- The TLF rate at 1 year was 7.8% in the Absorb arm and 6.1% in the Xience arm ($P_{non\text{-}inferiority} = 0.007$).
- One-year results for safety endpoints such as death, myocardial infarction and device thrombosis are summarized in **Table 1.3.2-2**. The observed rates were low overall with no statistical differences between the two device arms, demonstrating reasonable assurance of safety and effectiveness.
- Absorb demonstrated reasonable assurance of effectiveness, with ID-TLR rates comparable to Xience. Absorb preserves the effectiveness of current-day metallic DES compared to prior PCI treatments.
- In addition to Absorb showing non-inferiority in the overall population, the outcomes in the patient population closely aligned with the label (2.5 - 3.75 mm) provide evidence that when Absorb is placed in the appropriately sized vessels the differences between the two arms are further reduced.

1.3.1 ABSORB III Overview

The ABSORB III Randomized Controlled Trial (ABSORB III) was a prospective, multi-center trial with the primary objective of evaluating the safety and effectiveness of Absorb compared to Xience, the best-in-class DES, in the treatment of subjects with ischemic heart disease caused by up to two *de novo* native coronary artery lesions in separate epicardial vessels. The ABSORB III primary endpoint was non-inferiority of target lesion failure (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). TLF is prescribed in FDA guidance as the appropriate endpoint for use to evaluate DES. According to FDA guidance [2] and agreement with the FDA, a non-inferiority margin of 4.5% was selected for the primary endpoint, representing 50% of a conservative treatment effect estimate of 9% of Xience compared to the putative placebo of bare-metal stent (BMS). Details on the assumptions for the primary endpoint and the derivation of the non-inferiority margin can be found in **Section 5.1.7**. Pre-specified secondary endpoints that were adequately powered for analysis were angina at 1 year, all revascularizations at 1 year and ID-TVR at 1 year, all of which were designed to test the hypothesis that there may be a reduction in these endpoints with Absorb compared to Xience.

The Xience control used in the study was intentionally selected since it is one of the most safe and effective FDA approved DES. Xience has been evaluated in several large meta-analyses comprising of 125 randomized controlled trials with a total of 107,982 subjects [3, 4], and has been consistently shown in these meta-analyses to have lower event rates than other DES, including current generation DES on the market in the U.S. Therefore in the ABSORB III trial, the assessment of the 1 year safety and effectiveness of Absorb is in comparison to one of the best DES within PCI standard of care.

From March 2013 to April 2014, 2,008 subjects at 193 sites (191 sites in the US and 2 sites in Australia) were randomized to Absorb (N = 1,322) or Xience (N = 686). Three analysis populations have been evaluated in the ABSORB III study: the Intent-to-Treat (ITT) and Per-Treatment-Evaluable (PTE) populations, which were pre-specified in the protocol; and the As-Treated (AT) population, which was a post-hoc analysis. The ITT population (N = 2008) was comprised of all subjects randomized into the study regardless of the treatment actually received. Subjects in the ITT population were analyzed in the treatment group to which they were randomized. The PTE population (N = 1859) was comprised of subjects who received only study device(s) (Absorb or Xience) at the target lesion, but excluded those with specific protocol deviations to the eligibility criteria and treatment strategy that put them in a higher risk category. In the AT population (N = 1987), treatment group assignment was based on the treatment (Absorb or Xience) actually received. Subjects who received both Absorb and Xience in separate target lesions were included in the treatment group to which they were randomized. Subjects who received both Absorb and Xience in the same target lesion, and those who received no study device were excluded from the AT population.

From the ITT population to the AT population, there was a net reduction of subjects in the Absorb arm and a net increase in the Xience arm. The reduction in the Absorb arm was due to a combination of factors: crossover to Xience use, mixed use of devices (i.e. Absorb and additional device) on the target lesion, only non-study device used on the target lesion and no device implanted at the target lesion. The increase in the Xience arm was due to a combination of crossovers from the Absorb arm. There was also a reduction in the Xience arm due to mixed use of devices on the target lesion, only non-study device used on the target lesion and no device implanted at the target lesion. After accounting for the above factors and for terminations from the study, the number of subjects in the AT population was N = 1252 in the Absorb arm and N = 735 in the Xience arm.

From the ITT to PTE population, each device arm experienced approximately the same percentage of patients removed from the PTE population due to deviations meeting the specified PTE exclusion criteria (**Appendix 1**). In addition there was a reduction in number of Absorb subjects due to crossover to the Xience arm resulting in a PTE population of 1180 for the Absorb arm and 679 for the Xience arm.

Regardless of the difference in subject number between the ITT, AT and PTE populations, the study conclusions were not affected; clinical event rates were found to be similar between all three populations. Complete details on the ITT, AT, PTE population and the reason for subjects not receiving an assigned device can be found in **Sections 5.1.5** and **5.2.1**.

1.3.2 ABSORB III Key Study Results

The ABSORB III endpoints are summarized for the ITT analysis in this section. The outcomes for the PTE population and AT population were similar to the ITT population and are presented in **Section 5.2.2**. Except for the primary endpoint assessment in the AT population, shown in **Table 5.2.2-3**, the AT analysis presented in this document has not been reviewed by the FDA.

All baseline characteristics were well balanced between study arms in both ITT and AT populations. Key baseline demographics and risk factors are shown in **Section 5.2.1**.

Primary Endpoint

ABSORB III achieved its primary study objective, demonstrating non-inferiority in TLF at 1 year compared to Xience in the ITT population (**Table 1.3.2-1)**. The TLF rate at 1 year was 7.8% in the Absorb arm and 6.1% in the Xience arm. The Absorb arm was statistically non-inferior to Xience with a non-inferiority p-value of 0.007.

Table 1.3.2-1 Primary Endpoint Analysis – Per-Subject Analysis, Intent-to-Treat Population

Population	Absorb	Xience	Difference (95% CI)	Non-Inferiority P-Value
ITT	7.8% (102/1313)	6.1% (41/677)	1.7% (-0.5%, 3.9%)	0.007

The primary endpoint assessment in the PTE population, shown in **Table 5.2.2-2** located in **Section 5.2.2**, was consistent with the ITT population, with TLF rates at 1 year of 7.8% in the Absorb arm and 5.7% in the Xience arm (non-inferiority p-value = 0.018).

The primary endpoint assessment in the AT population, shown in **Table 5.2.2-3** located in **Section 5.2.2**, was consistent with the ITT population, with TLF rates at 1 year of 8.0% in the Absorb arm and 6.1% in the Xience arm (non-inferiority p-value = 0.011).

Subgroup analyses of the primary endpoint, as summarized in **Section 5.2.2**, showed similar clinical outcomes with no statistical differences in 1-year TLF between the Absorb and Xience arms for all pre-specified subgroups.

Other Safety and Efficacy Secondary Endpoints

One-year results for the component endpoints of TLF, as well as all death, all MI and device thrombosis are summarized in **Table 1.3.2-2**. The observed rates were low overall with no statistical differences between the arms, although the observed death, cardiac death, MI and TV-MI rates were numerically higher for Absorb compared to Xience. The small observed differences in cardiac death between two arms are not considered to be device related. As detailed in **Section 5.2.2**, the cardiac death rate of 0.6% for Absorb is comparable to historical rates between 0.4% and 0.9 % for Xience and other DES in recent trials with similar subject populations [5-9] while the Xience rate of 0.1% in ABSORB III is low compared to the Xience rates of 0.8%, 0.4%, 0.9% and 0.7% observed in the SPIRIT III (N = 655), SPIRIT IV (N = 2458), XIENCE V USA trials (N = 1839), and PLATINUM trials (N = 762), respectively.

TV-MI rates at 1 year showed that Absorb was associated with a 1.4% higher rate compared to Xience, with no statistical difference between arms. Also, device thrombosis rates at 1 year showed that Absorb was associated with a 0.8% higher rate compared to Xience, with no statistical difference between arms. Further analysis of the TV-MI and thrombosis rates found there was a strong dependence on reference vessel diameter (RVD), as described below in **Section 1.3.2.3**.

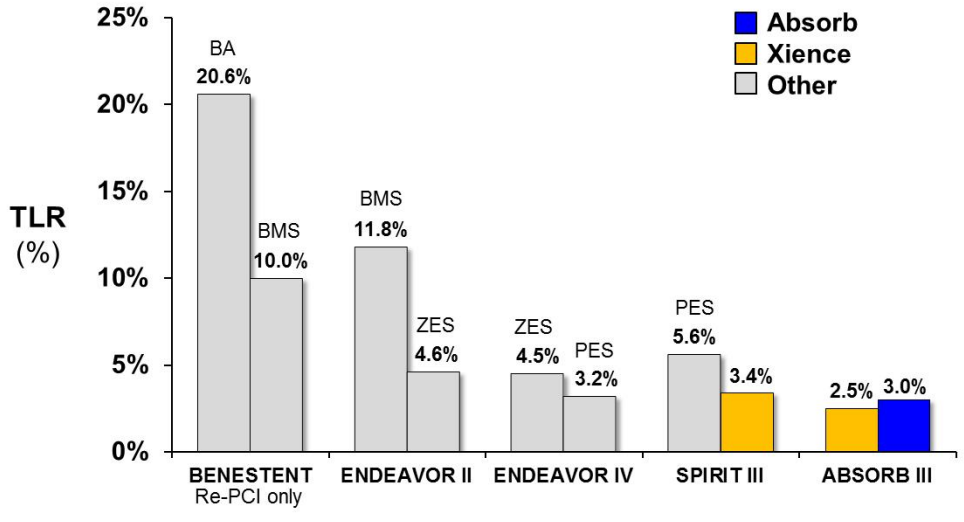
The efficacy assessment of ischemia-driven TLR (ID-TLR) rates were similar between the Absorb and Xience, with only a 0.5% observed difference (**Table 1.3.2-2)**. It is noteworthy that Absorb preserves the effectiveness of current-day metallic DES compared to prior treatments. **Figure 1.3.2-1** shows the evolution of TLR rates over the era of stenting,

beginning with the BENESTENT trial which evaluated bare metal stents (BMS) versus balloon angioplasty. The low revascularization rates of Absorb in ABSORB III represent a continuation in the efficacy profile offered by DES.

Table 1.3.2-2 ABSORB III Clinical Results (Intent-to-Treat Population) - 1-Year Results

	Absorb (N = 1322) (n/N)	**Xience (N=686)** (n/N)	**P-value***
All Death	1.1% (15/1313)	0.4% (3/677)	0.12
Cardiac Death	0.6% (8/1313)	0.1% (1/677)	0.29
All MI	6.9% (90/1313)	5.6% (38/677)	0.29
TV-MI	6.0% (79/1313)	4.6% (31/677)	0.18
QMI	0.7% (9/1313)	0.3% (2/677)	0.35
NQMI	5.3% (70/1313)	4.3% (29/677)	0.31
ID-TLR	3.0% (40/1313)	2.5% (17/677)	0.50
Cumulative ARC-defined Definite + Probable Stent/Scaffold Thrombosis (0-393 days)	1.54% (20/1301)	0.74% (5/675)	0.13

Note: 1-year timeframe includes a window of ± 28 days
Note: N is the total number of subjects
Note: MI is per protocol definition
*Not pre-specified and not adjusted for multiplicity



Note: ENDEAVOR II outcomes data represents at 270 days.

Figure 1.3.2-1 Evolution of PCI TLR Outcomes at 1 Year [6, 7, 10, 11]

Angina, ID-TVR, and all revascularization had a pre-specified evaluation for superiority based on signals of a possible advantage of Absorb compared to Xience in prior trials at 1 year (**Table 1.3.2-3**). Statistical significance was not observed between Absorb and Xience for these endpoints. However, the 1-year observations of angina and revascularization represent very good outcomes for both devices.

Table 1.3.2-3 Powered Secondary Endpoint Analysis – Per-Subject Analysis (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: For the angina endpoint, denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through 1 year without
any angina event. For the all revascularization endpoint, denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through 1 year without any DMR event (all death, all MI (regardless of MI definition), all revascularization, respectively).
Note: 1-year timeframe includes a window of +/- 28 days.
Note: N is the total number of subjects.

Reference Vessel Diameter Analysis

A post-hoc subgroup analysis was performed to assess the impact of vessel size on clinical performance. The current generation of Absorb has thicker struts than Xience (157 microns vs. 81 microns), and thus it is biologically plausible that in very small vessels, the space occupying effect of larger struts might negatively impact outcomes. The subgroup analysis compares event rates between very small vessels to vessels that are appropriately sized for

the intended study population. To be included in ABSORB III, subjects were required to have target vessels with a visually estimated RVD of ≥ 2.5 mm and ≤ 3.75 mm. Prior studies have shown that core laboratory-assessed QCA underestimates true vessel dimensions by approximately 0.25 mm compared to visual estimation [12]. Thus, the lower eligibility limit of 2.5 mm by visual estimation would correspond to 2.25 mm by core lab QCA, which was performed on all patients. Very small vessels where core lab RVD was < 2.25 mm are below the level intended for treatment in ABSORB III; notwithstanding this, baseline analysis showed that 18.8% of the study population had a lesion treated with RVD < 2.25 mm by core lab QCA.

Table 1.3.2-4 shows the event rates for key outcome measures for the RVD < 2.25 mm subgroup, the RVD ≥ 2.25 mm subgroup and the overall ITT study population. In subjects in which all lesions had an RVD ≥ 2.25 mm, most outcome measures, including device thrombosis, had lower observed rates in both Absorb and Xience arms and smaller differences between arms than in subjects with very small vessels and in the overall ITT study population. In both Absorb and Xience arms, there were higher observed event rates in the < 2.25 mm subgroup compared to the overall population. These findings are consistent with other DES trials in which very small vessels were treated and have important implications on the labeling of the device and physician education, which will be discussed further in **Section 8.0**. In addition, the findings from the RVD analysis demonstrate that, in addition to Absorb showing non-inferiority in the overall population, the outcomes in the subject population closely aligned with the label (2.5 - 3.75 mm) provide evidence that when the Absorb is placed in the appropriately sized vessels, the differences between the two arms are minimal.

Table 1.3.2-4 1-Year Clinical Outcomes Stratified by Core Laboratory Assessed RVD – Per-Subject Analysis (Primary Analysis Group, Intent-to-Treat Population, Per Protocol MI Definition)

	RVD < 2.25 mm*			RVD ≥ 2.25 mm			Overall ITT Population		
	Absorb (N=242)	Xience (N=133)	P-value**	Absorb (N=1074)	Xience (N=549)	P-value**	Absorb (N=1322)	Xience (N=686)	P-value**
TLF	12.9% (31/241)	8.3% (11/133)	0.18	6.7% (71/1067)	5.5% (30/542)	0.38	7.8% (102/1313)	6.1% (41/677)	0.16
Cardiac Death	0.8% (2/241)	0.0% (0/133)	0.54	0.6% (6/1067)	0.2% (1/542)	0.43	0.6% (8/1313)	0.1% (1/677)	0.29
TV- MI	10.0% (24/241)	4.5% (6/133)	0.06	5.2% (55/1067)	4.6% (25/542)	0.64	6.0% (79/1313)	4.6% (31/677)	0.18
ID-TLR	6.6% (16/241)	6.8% (9/133)	0.96	2.2% (24/1067)	1.5% (8/542)	0.29	3.0% (40/1313)	2.5% (17/677)	0.50
Device Thrombosis (Def/Prob)	4.6% (11/238)	1.5% (2/133)	0.15	0.9% (9/1058)	0.6% (3/540)	0.76	1.5% (20/1301)	0.7% (5/675)	0.13

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

** Not pre-specified and not adjusted for multiplicity

Diabetes Mellitus Subgroup Analysis

A pre-specified subgroup analysis was performed for diabetes mellitus. **Table 1.3.2-5** shows the key 1-year outcome measures for the overall ITT population, all diabetes mellitus (all DM) subgroup and all non-DM subgroup. Historically, diabetes mellitus is associated with elevated event rates in coronary stent trials, and the ABSORB III results are consistent with this pattern. For the all DM subgroup, the observed clinical event rates in both Absorb and Xience arms were higher than in the overall population for most key outcome measures, with similar proportional increases. Within both subgroups and the overall population, there were no statistical differences for any endpoint comparisons between study arms.

Table 1.3.2-5 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			Overall ITT population		
	Absorb (N=416)	**Xience (N=224)**	**P-value***	**Absorb (N=904)**	**Xience (N=462)**	**P-value***	**Absorb (N=1322)**	**Xience (N=686)**	**P-value***
TLF	10.7% (44/411)	9.1% (20/220)	0.52	6.3% (57/900)	4.6% (21/457)	0.19	7.8% (102/1313)	6.1% (41/677)	0.16
Cardiac Death	0.5% (2/411)	0.0% (0/220)	0.55	0.7% (6/900)	0.2% (1/457)	0.43	0.6% (8/1313)	0.1% (1/677)	0.29
TV- MI	9.0% (37/411)	7.3% (16/220)	0.46	4.6% (41/900)	3.3% (15/457)	0.27	6.0% (79/1313)	4.6% (31/677)	0.18
ID-TLR	5.6% (23/411)	3.6% (8/220)	0.28	1.8% (16/900)	2.0% (9/457)	0.80	3.0% (40/1313)	2.5% (17/677)	0.50
Stent/Scaffold Thrombosis (Def/Prob)	3.2% (13/405)	1.4% (3/219)	0.17	0.8% (7/894)	0.4% (2/456)	0.73	1.5% (20/1301)	0.7% (5/675)	0.13

*Not pre-specified and not adjusted for multiplicity

An assessment of diabetic results stratified by RVD showed that if appropriate vessel size is selected for treatment with Absorb, diabetic event rates are substantially reduced when compared to the overall diabetic population. As seen in **Table 1.3.2-6**, the observed clinical event rates in the Absorb and XIENCE arms were lower in the all DM with RVD ≥ 2.25 mm subgroup than in the all DM subgroup and all DM with RVD < 2.25 mm subgroup. An example is device thrombosis at 1 year, where the rates in Absorb and XIENCE arms of the all DM with all RVD ≥ 2.25 mm subgroup (1.3% vs. 0.6%) were substantially lower compared to all diabetics (3.2% vs. 1.4%) and to diabetics in the all DM with RVD < 2.25 mm subgroup (10.6% vs. 4.4%).

When compared to all thrombosis events in the ITT population of ABSORB III, the proportion occurring in very small vessel diabetic subjects is noteworthy. Of the 20 occurrences of thrombosis through 1 year for the Absorb arm in the overall ITT population, 45.0% (9/20) were in the all DM with RVD < 2.25 mm subgroup. Of the 5 occurrences of thrombosis in the Xience arm in the ITT population, 40.0% (2/5) were in the all DM with RVD < 2.25 mm subgroup. Therefore, in both device arms there were higher observed rates of thrombosis in diabetic subjects with very small vessels. Data must be taken into perspective given the small sample size of this analysis.

Table 1.3.2-6 Subgroup Information and 1-Year Clinical Outcomes Stratified by Diabetic Status and Core Laboratory Assessed RVD – Per-Subject Analysis (Primary Analysis Group, Intent-to-Treat Population, Per Protocol MI Definition)

	All DM			All DM with RVD ≥ 2.25 mm*			All DM with RVD < 2.25 mm		
	Absorb (N=416)	**XIENCE (N=224)**	**P-value****	**Absorb (N=325)**	**XIENCE (N=177)**	**P-value****	**Absorb (N=88)**	**XIENCE (N=45)**	**P-value****
TLF	10.7% (44/411)	9.1% (20/220)	0.52	7.2% (23/321)	7.5% (13/174)	0.90	23.9% (21/88)	15.6% (7/45)	0.27
Cardiac Death	0.5% (2/411)	0.0% (0/220)	0.55	0.3% (1/321)	0.0% (0/174)	1.00	1.1% (1/88)	0.0% (0/45)	1.00
TV- MI	9.0% (37/411)	7.3% (16/220)	0.46	6.2% (20/321)	6.9% (12/174)	0.77	19.3% (17/88)	8.9% (4/45)	0.12
ID-TLR	5.6% (23/411)	3.6% (8/220)	0.28	3.4% (11/321)	1.1% (2/174)	0.15	13.6% (12/88)	13.3% (6/45)	0.96
Stent/Scaffold Thrombosis (Def/Prob)	3.2% (13/405)	1.4% (3/219)	0.17	1.3% (4/318)	0.6% (1/173)	0.66	10.6% (9/85)	4.4% (2/45)	0.33

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

** Not pre-specified and not adjusted for multiplicity

A key finding of the subgroup analyses of the study population stratified by diabetes status and RVD, described further in **Section 5.2.2**, is that Absorb diabetic event rates in appropriately sized vessels are substantially reduced to the extent that they do not differ appreciably from Absorb non-diabetic event rates.

1.3.3 ABSORB III Conclusions

The primary endpoint for ABSORB III was met, as Absorb was non-inferior for the composite safety and effectiveness endpoint of TLF at 1 year compared to Xience. This satisfies the regulatory standard for DES approval by demonstrating a reasonable assurance of safety and effectiveness. Absorb was highly effective, with ID-TLR rates comparable to Xience. The strong results of ABSORB III trial were achieved with the first ever use of ABSORB by US physicians who had relatively limited usage (median of 2.0 devices per investigator) during the study. There were no statistical differences between Absorb and Xience for safety and effectiveness.

In the post-hoc RVD analysis, higher event rates were observed in both device arms when used in very small vessels (QCA RVD < 2.25 mm) but with a relatively greater increase in

events for Absorb compared to Xience. A similar result was also seen in the diabetic sub-group. To address these observed differences in all subjects with vessels < 2.25 mm, including diabetics, the Absorb label will include the following precaution and warning language:

Precaution:

> In small vessels (visually assessed as ≤ 2.75 mm), on-line QCA or intravascular imaging is strongly recommended to accurately measure and confirm appropriate vessel sizing (≥ 2.5 mm).

Warning:

> If quantitative imaging determines a vessel size < 2.5 mm, do not implant Absorb. Implantation of the device in vessels < 2.5 mm may lead to an increased risk of adverse events such as myocardial infarction and scaffold thrombosis.

In addition to the learnings from ABSORB III, as noted in **Section 7.0**, international experience indicates that optimal clinical outcomes are achieved with Absorb on good lesion preparation, accurate scaffold sizing and liberal performance of high pressure post-dilatation. As such, the Absorb Label will also include a recommendation on post-dilatation as shown below:

Precaution:

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

This language will be reinforced in the physician education program as further described in **Section 8.2**.

1.4 Supportive Clinical Studies Conducted Outside of the United States

Key Point:

- Long-term data from earlier trials with Absorb provides supporting information that after 1 year, Absorb accrues either similar or less TLF/MACE rates compared to Xience.

Clinical data on Absorb after 1 year can be used to support the evaluation of the device.

Currently there are two year data available from the ABSORB Cohort B, ABSORB EXTEND, and ABSORB II trials. In addition, data out to 3 and 5 years are also available from the ABSORB EXTEND and ABSORB Cohort B trials, respectively.

Two year TLF and scaffold thrombosis (ST) data from ABSORB Cohort B, ABSORB EXTEND and the ABSORB II trial were pooled. The average increase in TLF and ST across all three trials from 1 to 2-year was 2% and 0.5%, respectively, for Absorb. To put these data into perspective the increase in TLF and ST rates between 1 and 2-year for Xience in the SPIRIT III trial was also 2% and 0.35%, respectively. Refer to **Section 6.2** for complete data tables for each individual trial.

As further illustrated in **Section 6.3**, long-term data from earlier trials with Absorb provides supporting information that after 1 year, Absorb accrues either similar or less TLF/MACE rates compared to Xience.

1.5 Post-Approval Commitments

Abbott Vascular is committed to a robust post approval strategy, and has developed a post approval commitment plan. First, Abbott Vascular will continue to follow ABSORB III subjects through 5 years. Secondly, Abbott Vascular is also conducting ABSORB IV clinical trial which is designed to enroll 3,000 randomized subjects, of which more than1000 have been currently enrolled. ABSORB III and ABSORB IV clinical trial data will be pooled for a total of 5000 subjects with 5 year follow-up, powered to demonstrate superiority of Absorb to Xience. Third, Abbott Vascular is collaborating with FDA to construct a post-approval registry that will include approximately 2000 - 3000 subjects at approximately 150 - 200 sites. The study design would evaluate low frequency events, effectiveness of labeling, education for very small vessels (< 2.5 mm), and confirm generalizability of the treatment with Absorb to real-world practice. The estimated follow-up of safety and effectiveness would be approximately 5 years.

1.6 Benefit / Risk

Key Points:

- The ABSORB III trial met the primary endpoint, satisfying the FDA regulatory guidance for DES approval and thus, demonstrating a reasonable assurance of safety and effectiveness.
    - Absorb was non-inferior to standard of care Xience in the combined safety and effectiveness composite endpoint of TLF
- There were no statistical differences between Absorb and Xience for any of the safety and effectiveness endpoints.
- Absorb preserves DES treatment effect and performs like a DES in the first year.
- Outcomes in appropriately sized vessels (≥ 2.25 mm) representing >80% of study population (over 1600 subjects) are highly similar between Absorb and Xience:
    - TLF difference between Absorb and Xience 1.2%
    - TV-MI difference between Absorb and Xience 0.6%
    - ST difference between Absorb and Xience 0.3%
- These results were achieved despite physicians having limited experience implanting the study device. Results are expected to further improve as physicians gain more experience.
- The ABSORB III trial, by showing comparable safety and effectiveness rates to Xience, demonstrates that the benefits of Absorb outweigh the risks.

The ABSORB III trial met the primary endpoint, satisfying the FDA regulatory guidance for DES approval. This included Absorb being non-inferior to standard of care, Xience, in the combined safety and effectiveness composite endpoint of TLF at 1 year. There were no statistical differences between Absorb and Xience for safety and effectiveness. The outcomes of the ABSORB III trial demonstrate that Absorb preserves the effectiveness of DES over bare metal stent without leaving a permanent implant, and provides a reasonable assurance of safety and effectiveness. These results were achieved despite physicians having limited experience implanting the study device versus experience with thousands of Xience implants after 8 years of US approval. As is the case with other new technologies, results are expected to further improve as physicians gain more experience. This is supported by several trials and registries which identified that the continued use of optimal Absorb techniques has contributed to improved outcomes [13-16]. Most importantly, when implanted in appropriately sized vessels, Absorb had an even better safety profile, with lower and almost identical event rates to Xience. In the RVD ≥ 2.25 mm subgroup, the two devices

only had observed differences in TLF of 1.2%, TV-MI of 0.6%, and device thrombosis of 0.3%, all clinically similar between the two devices. These findings reinforce that when Absorb is placed in appropriately sized vessels, the benefits of Absorb at 1 year are comparable to that of Xience.

Specific to the efficacy endpoints, Absorb showed to have very low and similar ID-TLR rates compared to Xience, of 3.0% and 2.5%, respectively, preserving the expected effectiveness of DES over bare metal stents (BMS). Additionally, the powered secondary efficacy endpoints of angina, ID-TVR, and all revascularization were very comparable between the two devices, reinforcing the effectiveness of Absorb.

Long-term data from ABSORB Cohort B, EXTEND, and ABSORB II, described in **Section 6.2** and **6.3**, provide evidence that between 1 and 2 years the increase in event rates for Absorb is similar to that of historical Xience trials. Additionally, out to 3 and 5 years the rates of TLF and Major Adverse Cardiac Events (MACE, representing the composite of cardiac death, all MI and ID-TLR) for Absorb show an emerging trend for reduction as compared to Xience, consistent with what is expected given full resorption by 36 months. These long-term observations are to be further confirmed in the ABSORB IV trial but are not required for initial regulatory approval at 1 year.

In summary, the ABSORB III trial satisfies the regulatory requirements for DES approval and demonstrates that the benefits of Absorb outweigh the risks. This is further reinforced by the data which shows that when Absorb is placed in appropriately sized vessels its safety profile is improved compared to Xience. Absorb thus offers a new option for patients who need a safe and effective PCI, but who do not want a permanent implant.

2.0 Development Drivers for Technology

Key Points:

- Current DES are associated with persistence of late adverse events with an average annual increase of 2-3%, potentially caused by caging or impaired movement of the vessel.
- There is a need for new stent technology that:
  - restores vasomotion
  - allow for lumen enlargement
  - facilitates plaque regression
  - eliminates full metal jacket
  - eliminates permanent jailing of side branches
  - eliminates narrowing of the vessel when treating in-stent restenosis with a second metallic stent
  - eliminates blooming artifact in multislice computed tomography (MSCT) hindering analysis
- Absorb being a fully bioresorbable scaffold has the potential to offer these benefits.

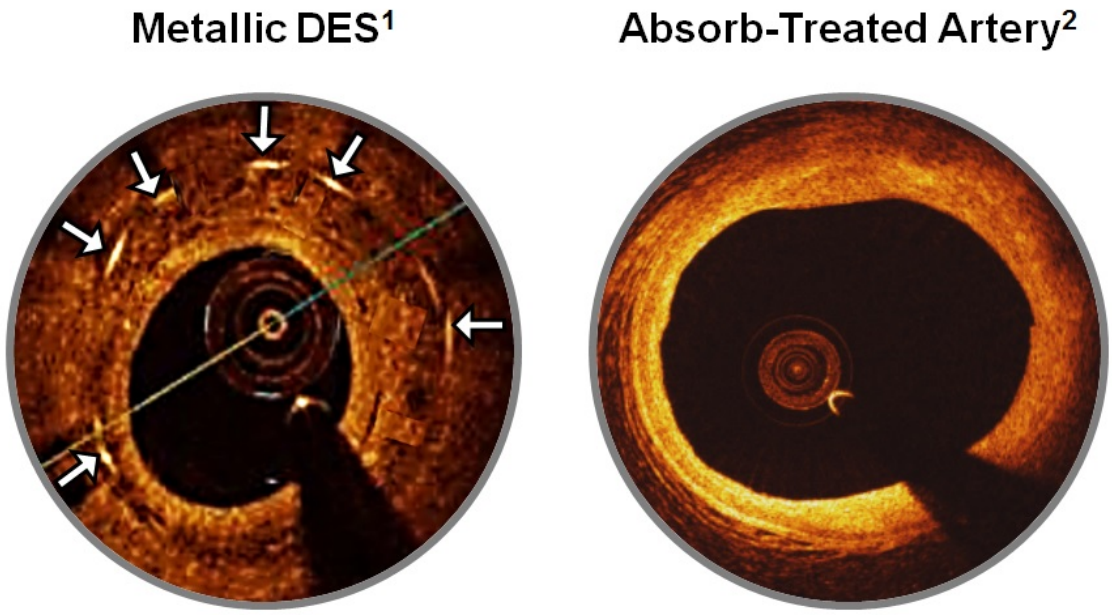
Over the last 20 years the outcomes for patients undergoing interventional cardiology procedures have continually improved as percutaneous coronary intervention (PCI) technology has matured from balloon angioplasty to bare metal stents to first generation drug eluting stents and now contemporary metallic drug eluting stents. Balloon angioplasty (BA) was a mechanical solution to treat coronary artery stenosis using an intra-luminal balloon to open a blocked artery. However, BA has limitations including intimal dissections, acute elastic recoil, abrupt closure and intimal remodeling. Bare metal stents (BMS), which are permanent implants, were developed in order to address some of BA's limitations. Drug-eluting stents (DES), coated with drugs to inhibit hyperplasia, were developed to address some of the limitations of BMS. Second-generation DES are currently the standard platform used for PCI. Among all available DES, Xience has demonstrated excellent performance based on several meta-analyses [3, 4, 17, 18]. However, both BMS and DES have presented with their own set of unique challenges such as intimal hyperplasia, stent thrombosis and long term event rates. In addition, there is a persistence of long-term target lesion failure (TLF) with a 2 - 3% per year increase between 1 and 5 years post-procedure [19] [20] [21]. These challenges have resulted in investigating whether the use of bioresorbable scaffold could be a potential solution to the late term events that can occur with metallic stents. The first step to addressing the persistence of long term events is to establish safety and effectiveness of Absorb at 1 year in order to make it available such that it can address metallic stents shortcomings in the long term.

One of the common denominators that could explain the late events with stenting appears to be the caging of the vessel, which can lead to loss of pulsatility and impaired healing [22]. Some of the causes of impaired healing include absence of cyclic pulsatility [23] and chronic inflammation [24]due to permanent foreign body reaction and/or hypersensitivity, which leads to uncovered stent struts [25] and neoatherosclerosis [26] [27], which then translates into thrombosis and restenosis events. Late strut fracture [28] [29] has also been associated with in-stent restenosis. The occurrence of these adverse effects can be associated with the presence of a permanent metallic implant in the artery.

Balloon angioplasty studies have demonstrated a coronary vessel free of a permanent implant is associated with reduced long-term events [30, 31]. Target lesion revascularization rates after 4 years, as well as late lumen loss (both early and long-term) are lower with balloon angioplasty (BA) as compared to metallic stents. The most stable very long-term outcomes, which are defined as greater than 10 years, were achieved in BA patients who had a low percent residual stenosis at index. A fully bioresorbable scaffold such as Absorb has the potential to replicate balloon angioplasty results through low residual stenosis at index, and mitigate some of the late undesirable effects seen with metallic stents, functioning like a DES early on, but leaving the vessel free of permanent implant once resorbed.

Late benefits offered by Absorb, such as restoration of pulsatility and vasomotion, lumen growth and plaque regression, have already been demonstrated in the ABSORB Cohort B trial. Cohort B was a first-in-man, single-arm, multi-center study with imaging modalities designed to study late lumen enlargement and vasomotor function following Absorb implantation. A total of 101 subjects, divided in 2 groups, were enrolled and followed up to 5 years. Group B1 underwent invasive imaging at 6, 24, and 60 months and group B2 had imaging at 12, 36, and 60 months. Imaging modalities were: OCT (Optical Coherence Tomography), IVUS (IntraVascular UltraSound) and QCA (Quantitative Coronary Angiography). More details on the results of the Cohort B trial can found in **Section 6.0**.

The OCT images below (**Figure 2.0-1**) of an Absorb-treated artery (subject from Cohort B) compared to a DES-treated artery [32] at 5 years illustrate the complete resorption of Absorb (the struts are no longer visible) and shows a vessel returned to its native state with healthy appearing tissue. Whereas in the DES-treated artery, stent strut are still visible and will remain in the artery for the lifetime of the patient.



1. Atherosclerosis 2014;237:23e29
2. Image courtesy of S Windecker, ABSORB Cohort B 5 Yrs

Figure 2.0-1 Five-Year OCT Images of Artery Implanted with Metallic DES (left) or Absorb (right)

Along with scaffold resorption and vessel healing, the ability of the vessel to move in response to physiological stimuli is restored (see **Section 6.4.3** for details of restoration of vasomotion). As the vessel heals, not only is it able to pulsate/dilate in response to stimuli, but late lumen enlargement and plaque regression have also been demonstrated in ABSORB Cohort B subjects (see **Sections 6.4.1** and **6.4.2** for more details). OCT images illustrating late lumen enlargement with Absorb are presented in **Figure 2.0-2**, below. Restoration of adaptive responses leading to increase in lumen diameter is not possible with metallic stents.

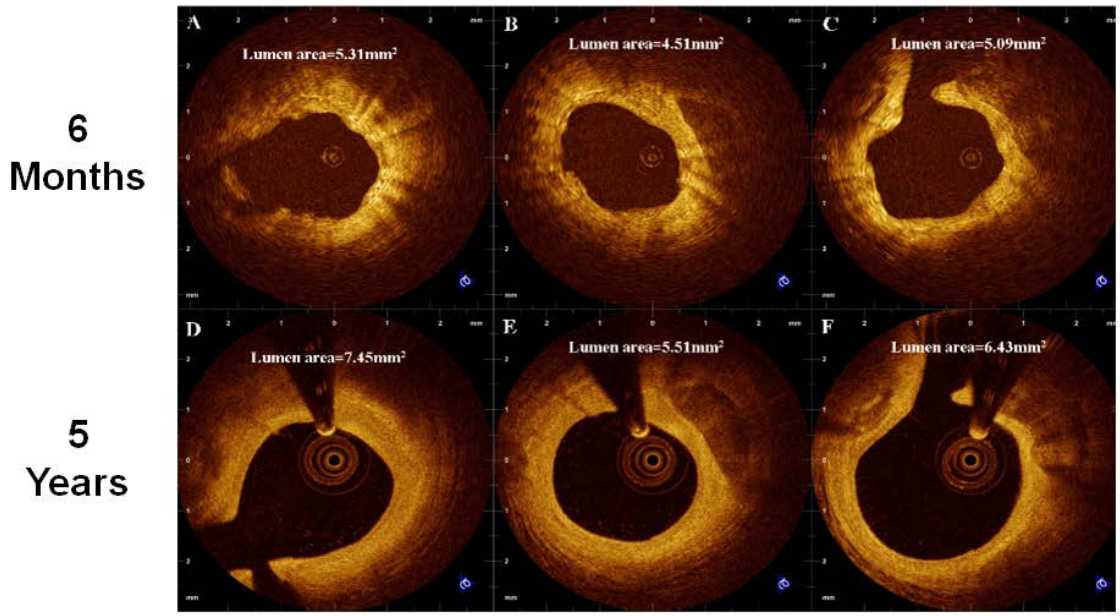
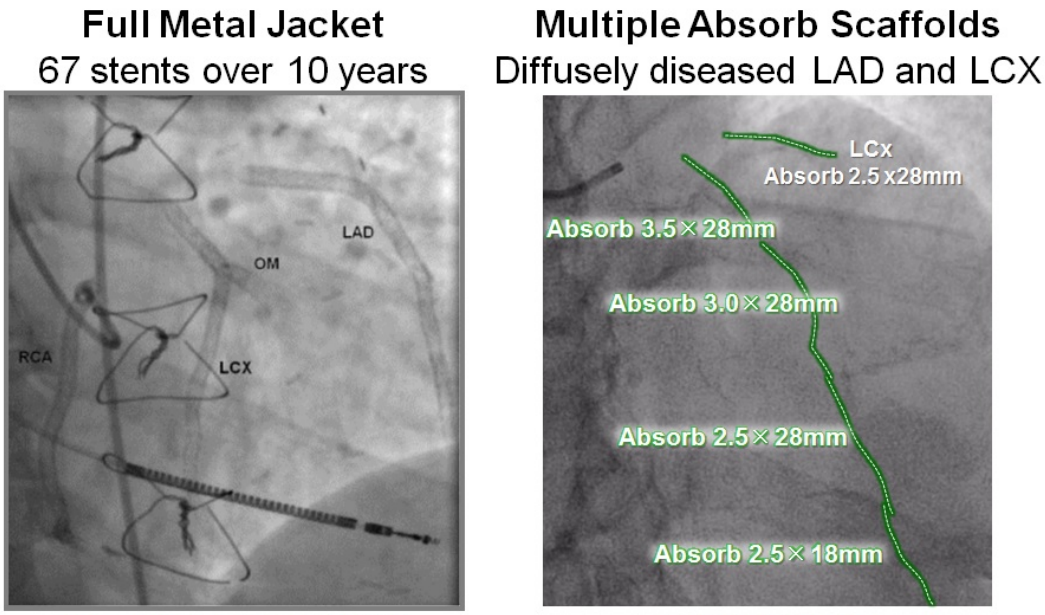


Figure 2.0-2 **OCT Images from Matched Sites at 6 Months (A-C) and 5 Years (D-F) after Absorb Implantation [33]**

There are also practical benefits of Absorb technology that could address shortcomings of metallic stents, such as:

- the so-called “full metal jacket”, which is defined as vessel lined up with metal stents in patients with long disease. **Figure 2.0-3** below presents an extreme case of a patient with chronic disease who was treated (outside of US) with 67 stents over 10 years [34]. In contrast, in the patient treated with 4 Absorb devices, no material is left in the vessel, except for the platinum markers, by approximately 3 years after Absorb implantation.
- permanent jailed side branches (refer to **Figure 6.4.2-2** in **Section 6.4.2)**.
- re-narrowing of the vessel when treating in-stent restenosis with a second metallic stent.
- blooming artifact in multislice computed tomography (MSCT) hindering analysis (refer to **Figure 6.5-1** in **Section 6.5**).



Note: Since Absorb resorbs overtime and is no longer visible, the location of Absorb devices is represented by the green lines.

Figure 2.0-3 Angiograms of a Patient Implanted with 67 Stents over 10 years versus a Patient Implanted with Multiple Absorb Scaffolds

In conclusion, contemporary DES have demonstrated good outcomes in the first year after implantation but are associated with ongoing chronic issues due to the effects from the permanent metal stent and polymer which last 20 years or longer. In addition, the permanent nature of metallic DES forever alters the coronary anatomy and impairs normal healing and vascular adaptive responses. Absorb was designed to achieve similar results as metallic DES during the first year, but with novel attributes supporting long-term healing. Absorb also affords physicians an expanded range of treatment options and greater flexibility to manage coronary artery disease, potentially improving late patient outcomes.

3.0 Regulatory & Development History

Key Points:

- Since receiving CE mark in 2010, Absorb has approved in over 100 countries worldwide, and more than 125,000 Absorb have been used commercially.
- Abbott Vascular is requesting approval of the Absorb GT1 BVS System which differs from the Absorb BVS System used in the ABSORB III RCT in the delivery system chassis only. The delivery system chassis was modified to improve deliverability. There were no changes to the implanted device (scaffold, drug coating, drug dose density and platinum marker beads) and the delivery system balloon.
- Absorb has been evaluated for safety in a comprehensive series of preclinical studies in porcine coronary arteries, with follow-up from 3 days to 48 months. These studies demonstrate the safety of Absorb relative to Xience, including bioequivalence of drug elution, comparable vascular responses, and complete degradation by approximately 36 months.

3.1 Regulatory History

The Absorb BVS System, the first fully bioresorbable vascular scaffold, received approval for commercialization in the European Union in December 2010. As of December 31, 2015, more than 125,000 Absorb BVS have been used commercially in over 100 countries around the world.

The Absorb BVS System is currently being studied in the ABSORB III clinical trial under an Investigational Device Exemption (IDE) in the United States. Additionally, clinical studies at various stages of long-term follow-up are continuing in Europe, Japan, China, Canada, and Australia.

The IDE for the ABSORB III clinical trial was first approved in December 2012. Abbott Vascular and FDA worked collaboratively to address a wide range of topics and question that were raised during the IDE. Following completion of the 1-year follow-up of the ABSORB III subjects, Abbott Vascular filed the PMA (P150023) for the Absorb GT1 BVS System in June 2015.

The only difference between the Absorb BVS System used in the clinical trial and the Absorb GT1 BVS System is the delivery system chassis which was modified to improve deliverability. There were no changes to the implanted device (scaffold, drug coating, drug dose density and platinum marker beads) and the delivery system balloon. The Absorb GT1

BVS System received CE mark in April 2015, and is approved for commercial use in over 75 countries as of December 31, 2015.

3.2 Device Development History

The ABSORB Cohort B trial, described further in **Section 6.0**, was conducted using the Absorb BVS System manufactured at Abbott Vascular's pilot manufacturing facility in Mountain View, CA. Only one scaffold design, used for both the 2.5 mm and 3.0 mm diameter product, was manufactured at this facility. When product manufacturing was transitioned from the pilot facility in Mountain View, CA to the full scale manufacturing facility in Temecula, CA, very minor enhancements were made to the scaffold pattern to increase manufacturability of the product. In addition, a medium design for 3.5 mm diameter product was added at this time. These devices were used in the ABSORB EXTEND, ABSORB II, ABSORB Japan, and ABSORB First trials, which are described in **Section 6.0**, and in the ABSORB III RCT trial which is described in **Section 5.0**. As the materials and fundamental controls (raw material, in-process, finished product) that dictate the performance profile of the Absorb scaffold (as discussed in **Section 4.5**) have remained constant and no significant change was made to the scaffold design, the data generated across all of these clinical trials is representative of the commercial product.

Abbott Vascular is requesting approval of the Absorb GT1 BVS System. The only difference between the Absorb BVS System described above and the Absorb GT1 BVS System is the delivery system chassis which was modified to improve deliverability. The implanted device (scaffold, drug coating, drug dose density and platinum marker beads) and the delivery system balloon are the same for both systems; therefore, the clinical results from the trials listed above are representative of the Absorb GT1 BVS System.

3.3 Preclinical Development

A comprehensive series of animal studies has been conducted to demonstrate *in vivo* safety and to assess the *in vivo* pharmacokinetics and degradation profiles of Absorb. These studies are summarized in **Table 3.3-1**.

Table 3.3-1 GLP Preclinical Studies Conducted for the *In Vivo* Evaluation of Absorb

Scaffold	Pharmacokinetics[1]	Degradation[2]	Safety[3]
Absorb BVS (mfg MTV)	Up to 90 days	28, 90, and 180 days; 12, 18, 24, 30, 36, and 42 months	3, 28, 90, and 180 days; 12, 18, 24, 30, 36, 42, and 48 months; 28, 90 day overlap
Absorb BVS (mfg TEM)	Up to 90 days and up to 300 days	--[4]	28, 90, and 180 days

Note: All studies conducted in porcine coronary arteries, using domestic swine for time points up to 90 days and Yucatan mini-swine for time points exceeding 90 days. Animals were on DAPT for time points up to 730 days. For safety studies, Xience served as the control device, with each animal receiving one Xience and either one or two Absorb as the anatomy allowed.

1 PK studies N = 6 - 9 Absorb
2 Degradation studies N = 8 - 14 Absorb
3 Safety studies N = 12 - 21 Absorb, 7 - 13 Xience or 12 overlap Absorb, 8 - 9 overlap Xience
4 Consistency in degradation results obtained in vitro for Absorb BVS (mfg MTV) and Absorb BVS (mfg TEM) indicate that these products are equivalent.

Collectively these *in vivo* animal studies demonstrate:

- An everolimus elution profile bioequivalent to Xience, and the systemic safety of everolimus covering the duration of the drug elution from immediately after implant to completion.
- Complete *in vivo* resorption of the Absorb scaffold by approximately 36 months.
- Consistency in the *in vivo* and *in vitro* degradation profiles of the Absorb scaffold as based on number average molecular weight (M_n), confirming that degradation is hydrolytically driven.
- The acute, subchronic, and chronic safety and *in vivo* biocompatibility of the Absorb scaffold throughout *revascularization* (to 180 days), *restoration* (180 days to approximately 18 months), and *resorption* (approximately 18 months to approximately 36 months) phases and beyond to 48 months.
- The unique attributes in the vascular response to the Absorb scaffold, including benign expansive remodeling, lumen gain, and the restoration of pulsatility in Absorb-implanted arteries, which were observed progressively from approximately 12 months to 48 months. Additionally, the restoration of vasomotion was demonstrated at 1 and 2 years follow-up in Absorb-implanted porcine coronary arteries [35].

4.0 Product Overview

Key Points:

- The Absorb GT1 Bioresorbable Vascular Scaffold System is composed of the following components:
    - A bioresorbable poly(L-lactide) (PLLA) scaffold backbone
    - A coating comprised of the active pharmaceutical ingredient everolimus (100 µg/cm^2 drug dose density) 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 stent delivery systems, and incorporates design features from Absorb BVS, Xience Xpedition®, and Xience Alpine® delivery systems
- The performance of Absorb evolves over time, and is defined by three phases of revascularization, restoration, and resorption.
    - During revascularization, Absorb performs similarly as a permanent DES, restoring vessel patency and having controlled elution of everolimus to suppress restenosis.
    - Over the course of restoration and resorption, Absorb gradually transitions to a passive implant, allowing for the vessel to undergo adaptive remodeling and resume vasomotion.
- Preclinical studies have demonstrated comparable safety of Absorb to Xience through each of these three performance phases as well as the observations unique to Absorb of adaptive remodeling and restored pulsatility and vasomotility.

Absorb is a first of its kind fully bioresorbable drug eluting scaffold for use in the coronary vasculature. The bioresorbable polymer poly(L-lactide) (PLLA) scaffold is coated with a blend of the antiproliferative drug everolimus and bioresorbable polymer poly(D,L-lactide) (PDLLA) and pre-mounted on a rapid exchange (RX) scaffold delivery system. Xience, with its proven excellence in safety and effectiveness, was used as the basis for the development of the Absorb GT1 BVS System.

The product sizes for Absorb are detailed below in **Table 4.0-1**. The small design is available in 2.5 and 3.0 mm diameters and in lengths of 8, 12, 18, 23, and 28 mm. The medium design is available in a 3.5 mm diameter and in lengths of 12, 18, 23, and 28 mm.

This section provides an overview of the product design, principles of operation, and the performance goals of the product.

Table 4.0-1 Absorb Size Matrix

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

4.1 Scaffold Design

The scaffold design of Absorb was based on the design of the Xience family of products. It is comprised of a series of circumferentially-oriented sinusoidal rings that open during expansion to support the vessel and restore patency. Each ring is connected to neighboring rings by three linear links. Two scaffold designs are utilized across the Absorb product matrix. The small design is employed for the 2.5 and 3.0 mm diameter sizes, while the medium design is employed for the 3.5 mm diameter sizes. Both scaffold designs are based upon the same principles as Abbott Vascular's metallic balloon expandable stents (Multi-Link and Xience family of products), with permanent deformation of the device being achieved by permanent deformation of the ring structure. As the scaffold material is not radiopaque, two platinum markers are embedded at each end ring to enable fluoroscopic visualization. **Figure 4.1-1** contains photographs of the small Absorb scaffold in its crimped and expanded state.

A. B.

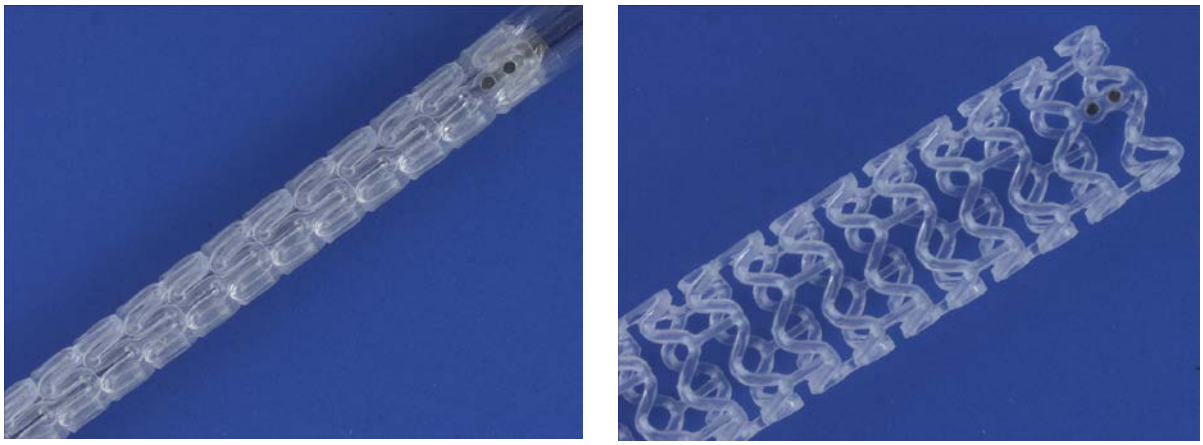


Figure 4.1-1 Photographs of the 3.0 mm Small Absorb Scaffold in A) Crimped and B) Expanded Forms

4.2 Scaffold Drug Coating

The drug coating for the Absorb scaffold is based on the drug coating for the Xience family of products, where an amorphous polymer is used to contain and control the release of the active pharmaceutical ingredient everolimus. For Absorb, the fully bioresorbable polymer poly(D,L-lactide) (PDLLA) is used for the drug coating. PDLLA is a random copolymer with equimolar subunits of D- and L-lactic acid which degrades through hydrolysis to carbon dioxide and water. (Refer to **Section 4.4** for a more detailed discussion regarding degradation). Absorb utilizes the same drug dose density (100 $\mu g/cm^2$) and similar coating technologies, replicating the drug release rate of the Xience family of products.

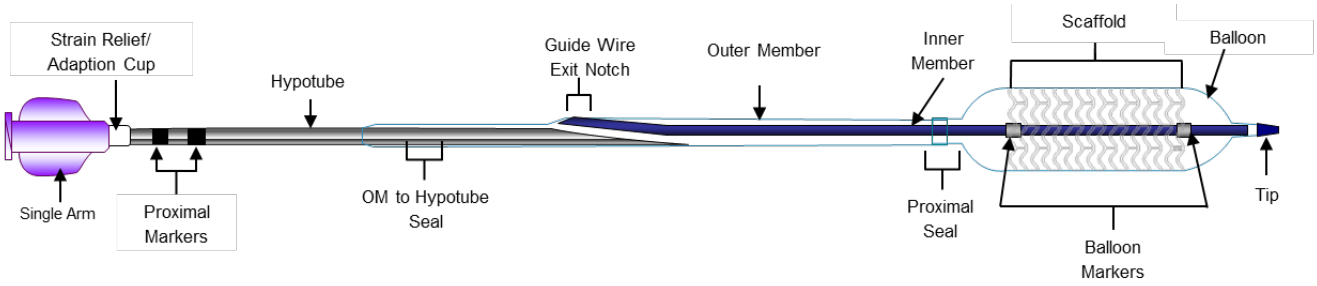
4.3 Optimized Delivery System

The optimized delivery system (ODS) utilized for the Absorb GT1 BVS System incorporates design features from the Xience V / Absorb BVS[1], Xience Xpedition, and Xience Alpine delivery systems. The ODS is intended to improve the existing technology of the Absorb BVS delivery system to align with the current Xience family of products, enhancing deliverability while improving manufacturability.

The ODS is a rapid-exchange (RX) design with the balloon and scaffold at the distal end of the catheter. With 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. The components of the ODS are shown schematically in **Figure 4.3-1**.

[1] The Xience V and Absorb BVS delivery systems are identical in design, materials, and performance, with minor dimensional adjustments to accommodate the Xience stent or Absorb scaffold, to that of the Multi Link Vision® Rapid Exchange (RX) Coronary Stent System (CSS) and Multi Link Vision® CSS



Note: Drawing not to scale

Figure 4.3-1 Components of the Optimized Delivery System for Absorb

4.4 Scaffold Backbone Polymer

The Absorb scaffold backbone is manufactured from the bioresorbable polymer poly(L-lactide) (PLLA), a semicrystalline polymer whose degree of crystallinity and crystalline microstructure are governed by the manufacturing process. The high tensile strength and modulus of PLLA make it suitable for load bearing applications.

Bioresorbable polymers have been the subject of extensive scientific research and commercial development in fields as diverse as food packaging and biomedical devices. Polylactide (PLA) and its copolymers have a long history of use in medical devices starting with bioresorbable sutures in the 1960s.

PLA degrades through hydrolysis to lactic acid. This process is not enzymatically or tissue driven and is dependent solely on the presence of water. Therefore, the rate of degradation is consistent between animals, humans, and varying diseases states. The chemical reaction shown in **Figure 4.4-1** portrays the hydrolysis reaction in which water causes chain scission at the ester bond of PLA. Consequently, the PLLA and PDLLA in the Absorb scaffold degrade to L- and D-lactic acid, which is readily converted to lactate. Lactate is in turn metabolized into carbon dioxide and water via the Krebs Cycle and also serves as a source of energy in anaerobic metabolism. The pKa of L-lactic acid is 3.4; hence, at physiological conditions, it readily dissociates into L-lactate and protons (H^+) [36]. L-lactate participates as an intermediary in numerous metabolic processes, including aerobic and anaerobic metabolism and as mediator of redox state among various compartments both within and between cells.

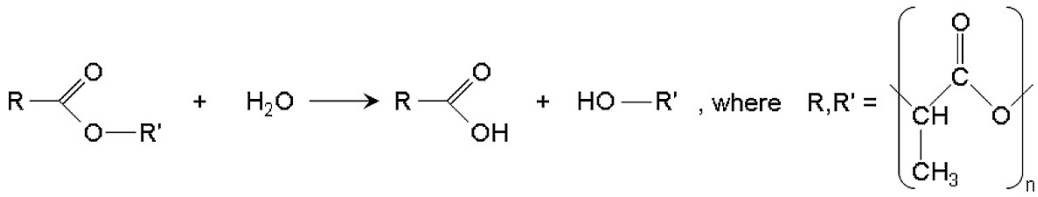
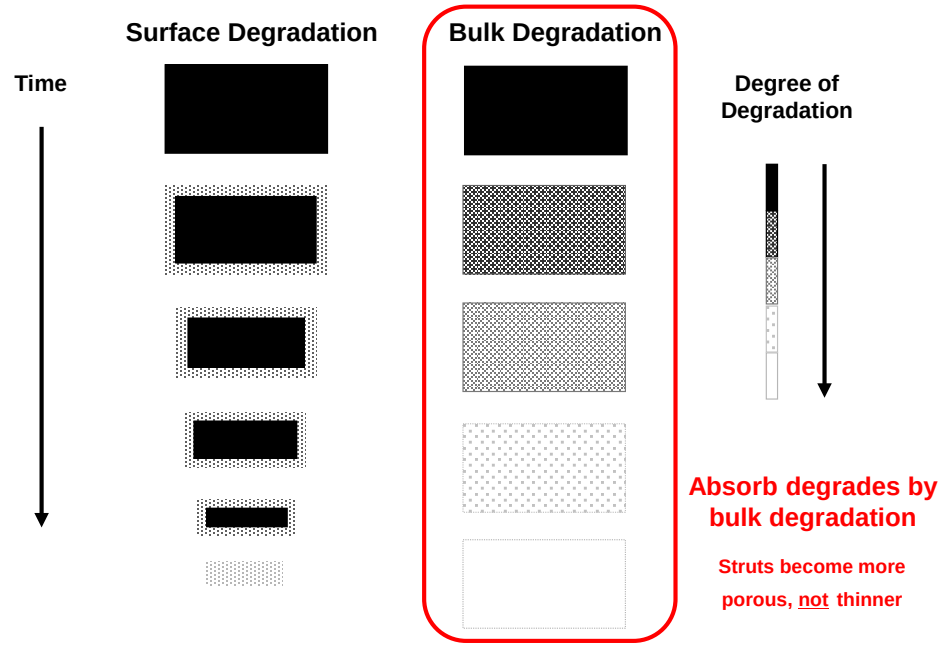


Figure 4.4-1 Reaction Pathway for Hydrolytic Degradation of PLA

The degradation process for the Absorb scaffold is a bulk degradation process with degradation occurring uniformly throughout the scaffold strut rather than only at the surface. In the case of surface degradation, the strut would become smaller with time. Due to the bulk degradation process of the Absorb scaffold, the struts become more porous, not smaller, with time. **Figure 4.4-2** is a schematic representation of bulk degradation versus surface degradation. Because bulk degradation governs hydrolysis of the Absorb scaffold [37], the degradation profile is not influenced by scaffold size and is consistent across the product size matrix.



Note: Absorb degrades by bulk degradation, which is not influenced by scaffold size. The degradation profile is therefore consistent across the product size matrix.

Figure 4.4-2 Absorb Degrades by Bulk Degradation [37]

4.5 Absorb Principles of Operation and Performance Goals

Absorb is designed to revascularize obstructed coronary arteries and ultimately restore the implanted vessel to an unconstrained state. The performance of Absorb evolves with time after implantation, and the ensuing discussion offers an overview of that time-dependent performance profile.

The performance of Absorb is described by three phases that span its lifecycle, namely *revascularization*, *restoration*, and *resorption* (see **Figure 4.5-1**). These phases parallel the generalized description of degradation for the aliphatic polyester family of materials of which polylactide (PLA) is a part, where molecular weight, strength, and mass successively begin to decline [38, 39]. The initial molecular weight and the rate of molecular weight degradation govern the time scales associated with loss of support and loss of mass, where the degradation rate occurs *in vivo* and *in vitro* through hydrolysis [40].

Each of these phases and their associated performance goals will be described in the sections below.

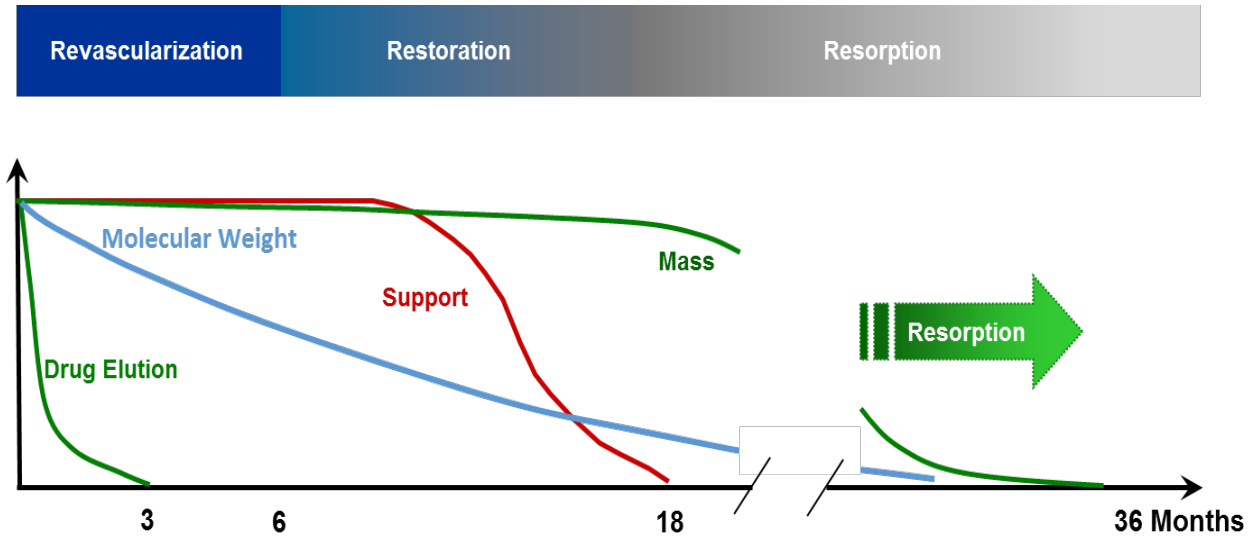


Figure 4.5-1 Schematic Drawing of the Three Phases of Absorb Performance

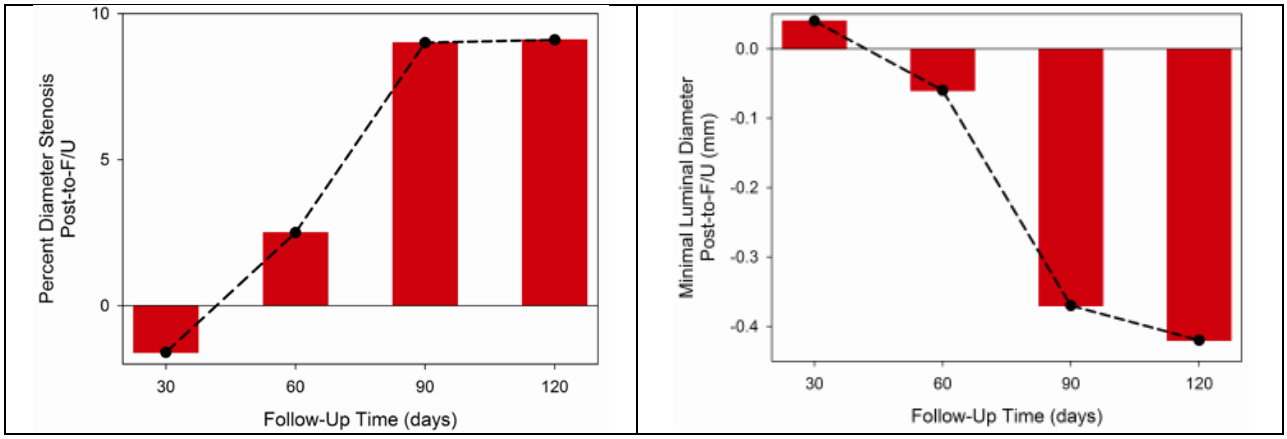
4.5.1 Revascularization Phase

The revascularization phase is the phase in which Absorb is designed to perform similarly to a metallic drug eluting stent. For Absorb, this phase is the time from implantation through 6 months.

During this phase, a principal design objective of Absorb is to maintain vessel support for a minimum of 3 months in order to minimize constrictive remodeling of the vessel and maintain lumen patency until the vessel has stabilized following revascularization. Clinical data for the mean lumen diameter and percent diameter stenosis after percutaneous transluminal coronary angioplasty (PTCA) via serial angiography indicates that vessel support need only be provided for approximately three months for the vessel lumen to stabilize [41].

Illustrated in **Figure 4.5.1-1**, after PTCA, the treated segment lumen stabilizes by approximately 3 months. After this time, there is no significant loss in luminal diameter. Therefore, the mechanical support provided by a scaffold/stent is only required for approximately 3 months after which the device serves no mechanical purpose. Absorb provides temporary mechanical support of the treated vessel segment for a minimum of 6 months, exceeding the 3 month time period where the vessel requires this support.

During this phase, Absorb releases everolimus at a rate that will inhibit smooth muscle cell proliferation while allowing for endothelialization and the controlled formation of neointima to cover struts prior to the scaffold's eventual loss of continuity.



N = 342 subjects (N = 93 at 30 day follow-up; N = 79 at 60 day follow-up; N = 82 at 90 day follow-up; and N = 88 at 120 day follow-up.)

Figure 4.5.1-1 Quantitative Angiographic Study in 342 Consecutive Subjects at 30, 60, 90 and 120 Days Post PTCA [41]

As demonstrated through preclinical and in vitro testing, Absorb maintains structural integrity throughout the 6 months of the revascularization phase. This assures neointimal coverage of the scaffold struts prior to the scaffold's eventual loss of continuity. As demonstrated by optical coherence tomography (OCT) in the ABSORB Cohort B trial (paired analysis, N = 23), 98% of struts were covered by neointima by the 6 month time point.

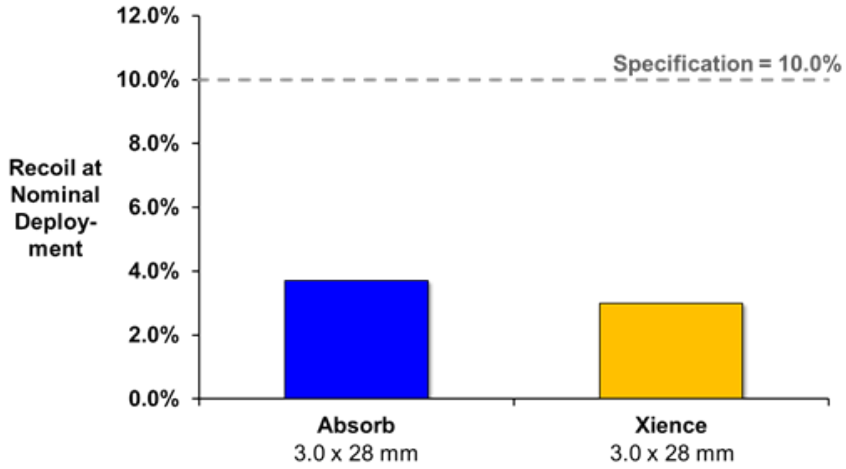
The performance goals for Absorb during the revascularization phase are to perform similarly to the Xience family of products in terms of recoil, radial strength, drug delivery, conformability, and vessel healing. Details as to how Absorb has met each of these goals are covered in the sections below.

Recoil

Minimizing acute scaffold recoil ensures that the final deployed diameter of a scaffold is representative of the labeled diameter of the scaffold and delivery system. Moreover, low recoil improves apposition to the vessel wall, providing the appropriate geometry for vessel support and limiting acute lumen area loss.

Historical data on metallic stents has been used to establish Absorb recoil requirements. Carrozza *et al*. [42] reported that a deployed diameter ratio of 1.1 to 1 is necessary to achieve a final stent-to-artery ratio of 1 to 1, suggesting that 10% recoil is clinically acceptable. Therefore, Absorb meets the recoil specification of less than or equal to 10%.

The recoil of Absorb as tested on the bench is similar to that of the Xience family of products as demonstrated in **Figure 4.5.1-2**, below.



Note: Data presented is mean of N = 10 for both Absorb and Xience.

Figure 4.5.1-2 Acute Recoil Bench Test Data for Absorb and Xience

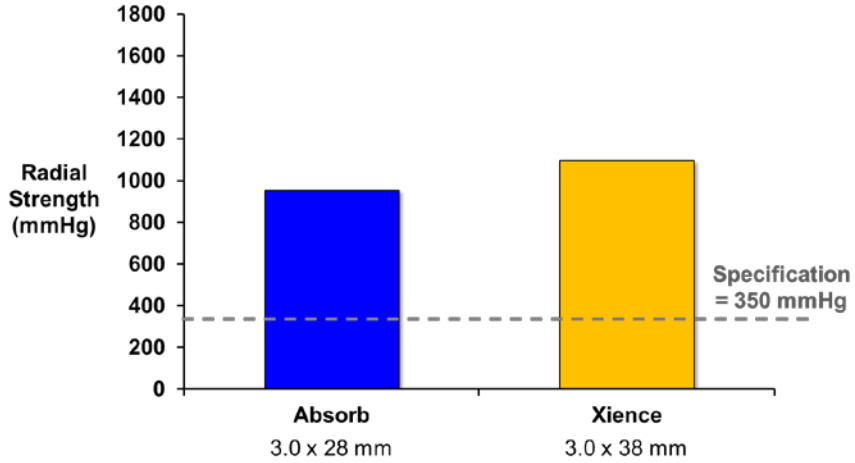
Radial Strength

A principal design objective of the Absorb scaffold is to maintain vessel support for a minimum of 3 months in order to minimize constrictive remodeling of the vessel and maintain lumen patency until the vessel has stabilized following revascularization [41]. Radial strength is the attribute that describes the scaffold's ability to support the vessel.

Agrawal *et al*. [43] reported a maximum vessel spasm transmural pressure of 175 mm Hg for a polymeric stent as derived from the maximum constriction pressure that a vessel could exert on a stent due to vessel spasm. The Absorb scaffold radial strength specification was established by applying a conservative safety factor of 2.0 to the maximum pressure of 175 mm Hg, resulting in a value of 350 mm Hg.

Unlike a DES, the ability of a BVS to support a vessel is expected to dissipate as its material degrades. Hence, it is necessary to characterize the Absorb scaffold radial strength not only acutely after deployment but also throughout its degradation to demonstrate that the scaffold provides sufficient vessel support for a minimum of 3 months.

The Absorb scaffold provides similar vessel support as is provided by the Xience family of products from initial deployment through 6 months. Results from bench testing of radial strength for Absorb and Xience at time of initial deployment are presented in **Figure 4.5.1-3**, below. In addition, Absorb shows no decline in radial strength after the equivalent of 6 months of testing under simulated *in vivo* degradation and loading conditions.



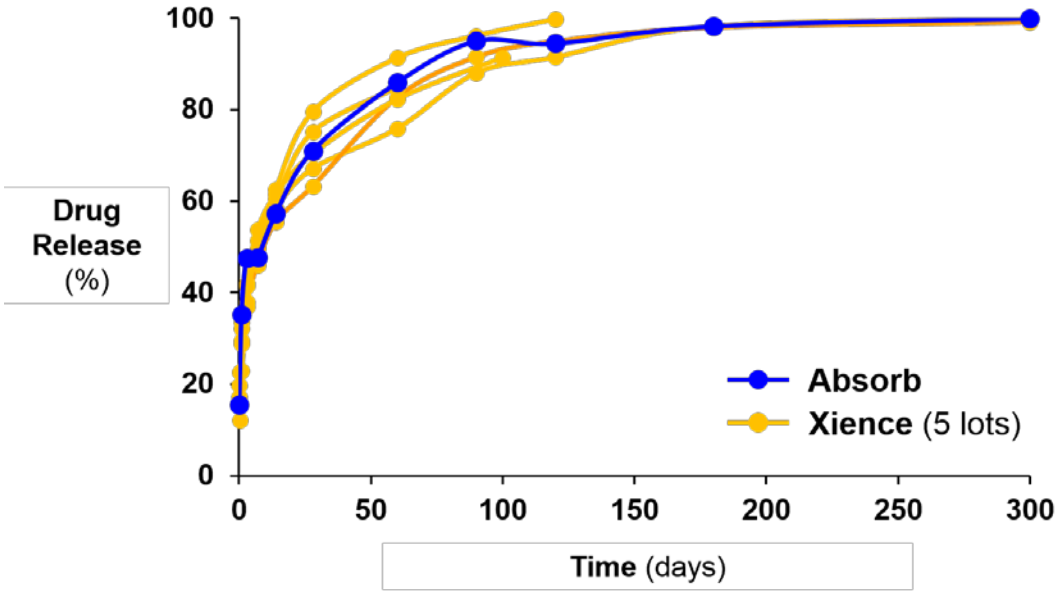
Note: Data presented is mean of N = 33 for Absorb and N = 30 for Xience

Figure 4.5.1-3 Radial Strength Bench Data for Absorb and Xience

Drug Release Profile

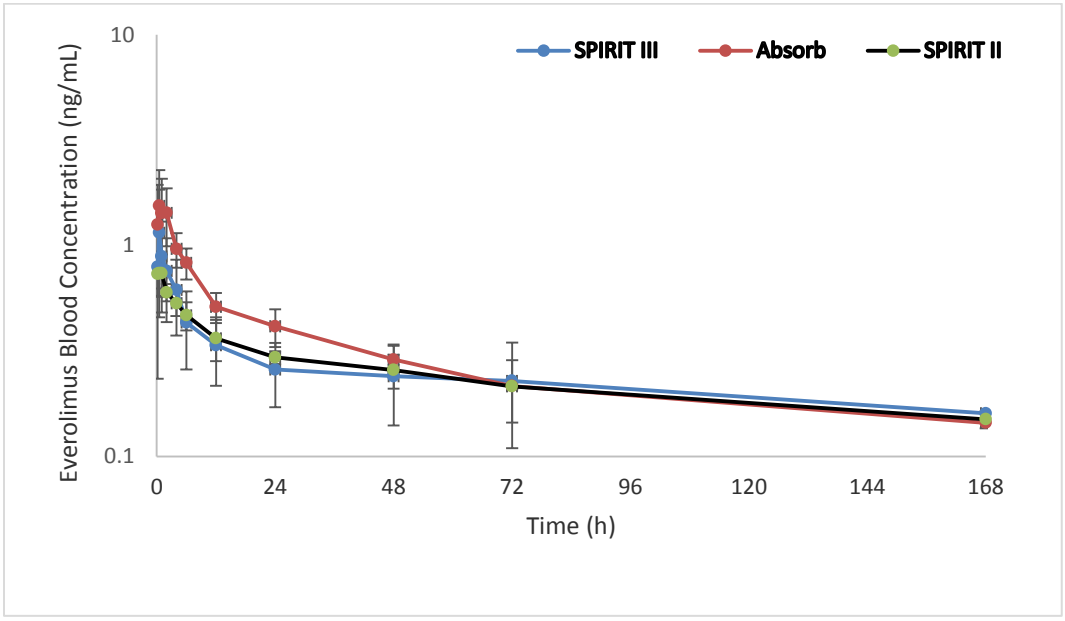
The everolimus drug release profile from the Absorb coating is designed to inhibit smooth muscle cell proliferation while allowing for endothelialization and controlled neointimal formation to cover struts. Guided by the safety and effectiveness demonstrated by Xience V in the SPIRIT family of clinical trials, Absorb replicates the drug dose density and drug release profile of the Xience family of products.

The drug release profile for Absorb and the Xience family of products are bioequivalent, as can be seen in comparison of preclinical drug release data in **Figure 4.5.1-4**. The equivalence between Absorb and the Xience family of products is further supported by the data for human everolimus blood concentration in **Figure 4.5.1-5**. Further information on Absorb human pharmacokinetics can be found in **Section 5.4**.



Note: Data presented are mean ± SD of the Absorb and means of 5 lots of Xience V. Data obtained in porcine coronary arteries. N = 6 - 9 per evaluation time point.

Figure 4.5.1-4 Preclinical Cumulative % Drug Release Profiles of Absorb and Xience V

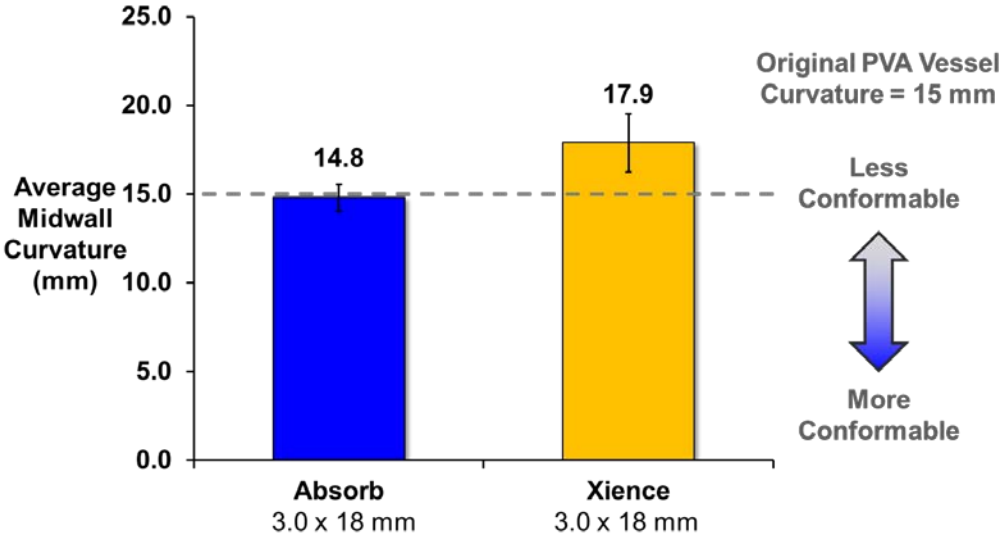


Note: Mean (± SD) whole blood concentration-time data after a 181 µg dose from a total of 13 subjects from the SPIRIT II (Xience, N = 4), SPIRIT III (Xience, N = 6) and ABSORB III (Absorb, N = 3) studies

Figure 4.5.1-5 Mean Whole Blood Concentration-Time Curves of Everolimus - Absorb and Xience V (SPIRIT II, SPIRIT III)

Conformability

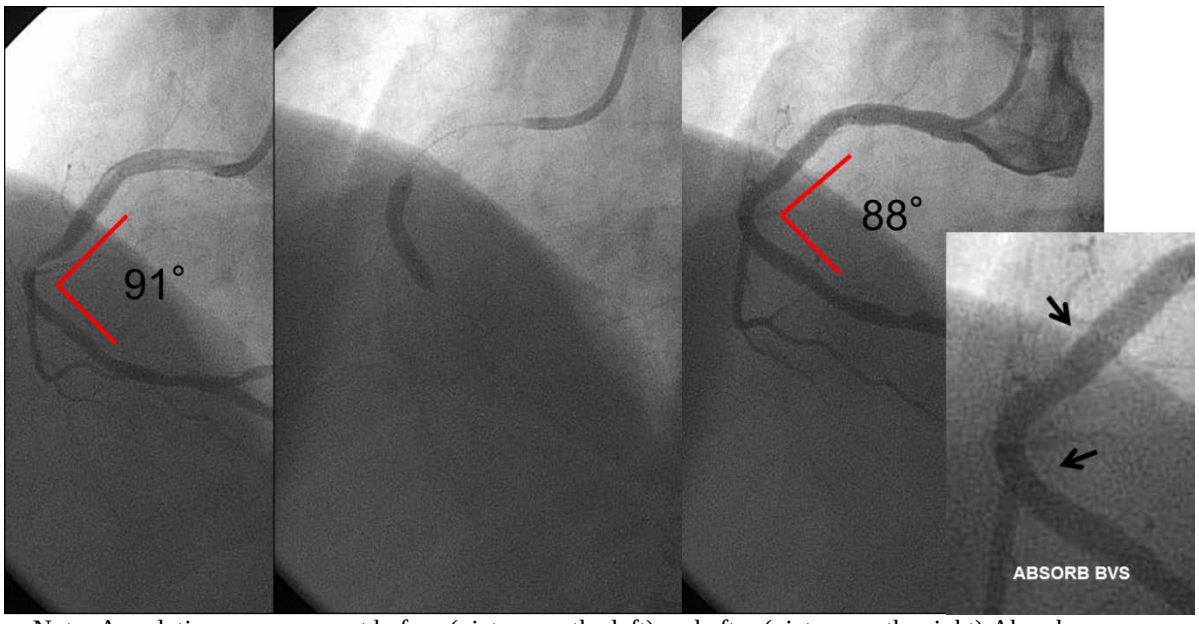
Conformability is the ability of a stent or scaffold to conform to the vessel geometry. A stent/scaffold that straightens out the vessel is considered less conformable than a stent/scaffold that retains the natural curvature of the vessel. The Absorb scaffold is highly conformable and provides improved vessel conformability as compared to the Xience family of products. As demonstrated by the bench test data for vessel straightening in **Figure 4.5.1-6**, the Absorb scaffold conformed better and impacted vessel curvature less than Xience. Conformability was tested using curved poly(vinyl alcohol) (PVA) vessels and measuring the midwall radius of curvature after deployment. A larger radius of curvature value indicates a stiffer and less conformable stent/scaffold. The unstented/unscaffolded radius of curvature of the PVA vessel was 15.0 mm.



Note: Data presented are mean ± SD for N = 6 for both Absorb and Xience.

Figure 4.5.1-6 Absorb and Xience V Average Midwall Radius of Curvature after Deployment

Clinically, a retrospective study, aimed at assessing the differences in curvature and angulation of the treated vessel was conducted in 191 subjects: 102 subjects from the SPIRIT First and SPIRIT II trials who received metallic platform stents (Multi-Link Vision or Xience V), and 89 subjects from the ABSORB Cohort B trial who received Absorb [44]. Data from this study showed less change in vessel curvature and lower modification of vessel angulation upon Absorb implantation as compared to Xience V. These results support that Absorb has a better conformability than Xience V. **Figure 4.5.1-7**, below, illustrates the small change in vessel curvature observed after implantation of Absorb.

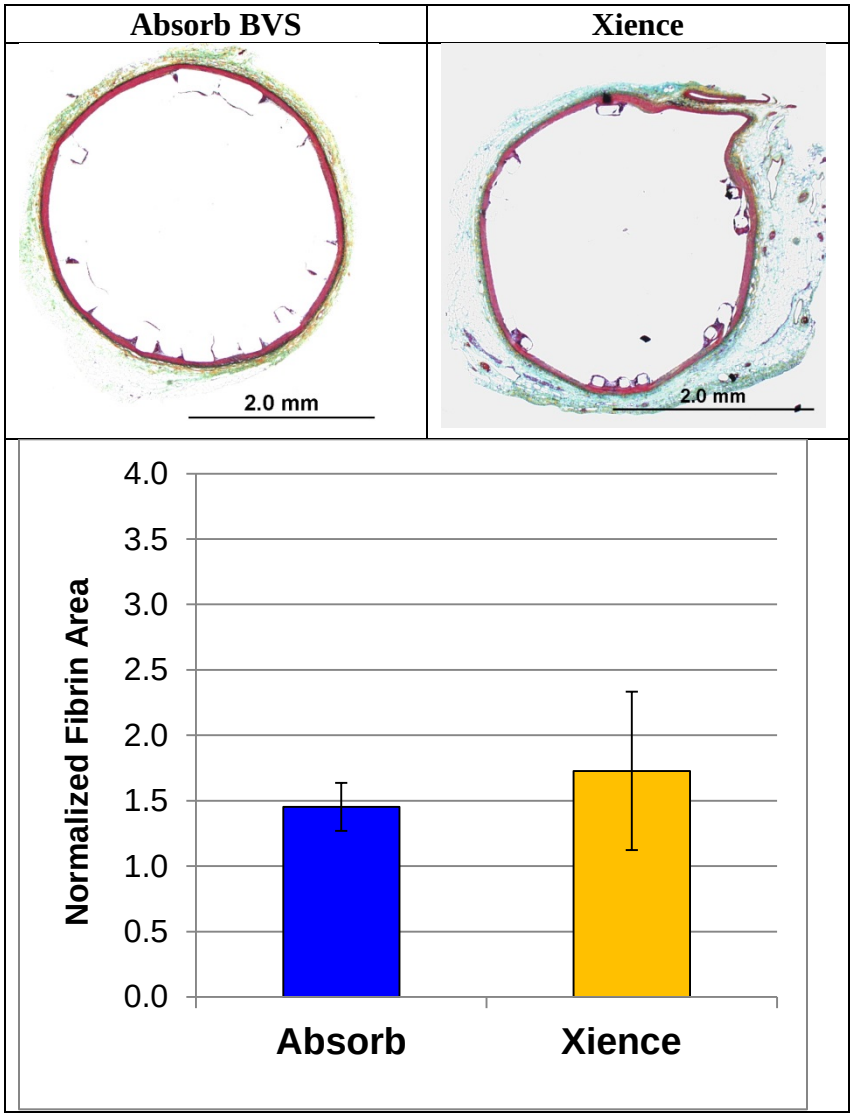


Note: Angulation measurement before (picture on the left) and after (picture on the right) Absorb implantation

Figure 4.5.1-7 Absorb Conformability [45]

Vessel Healing

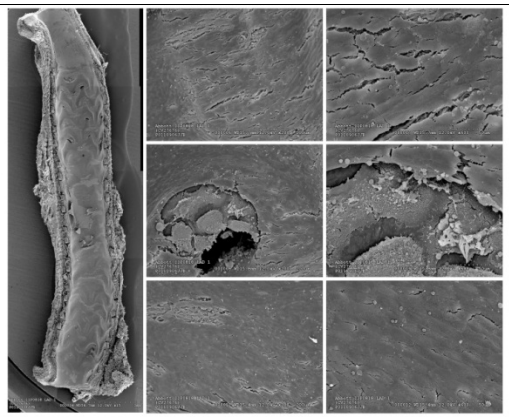
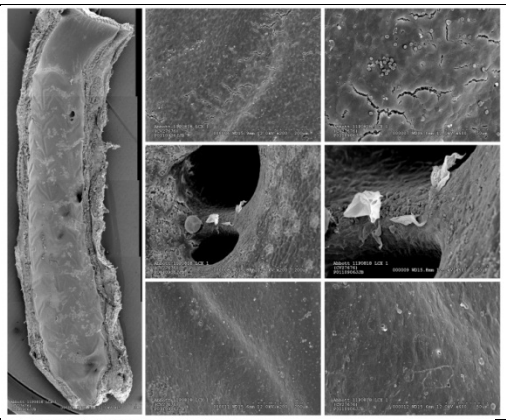
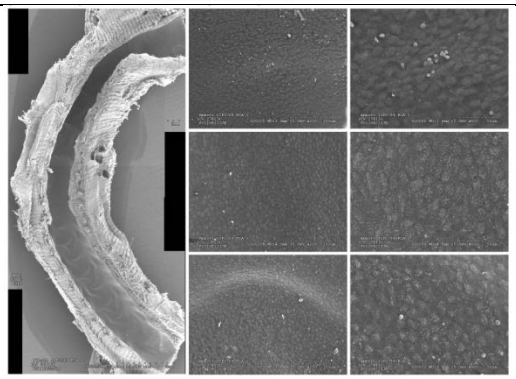
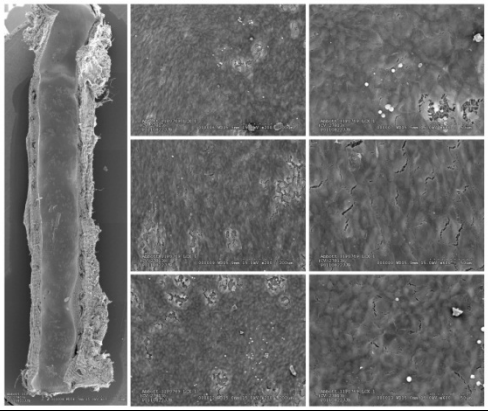
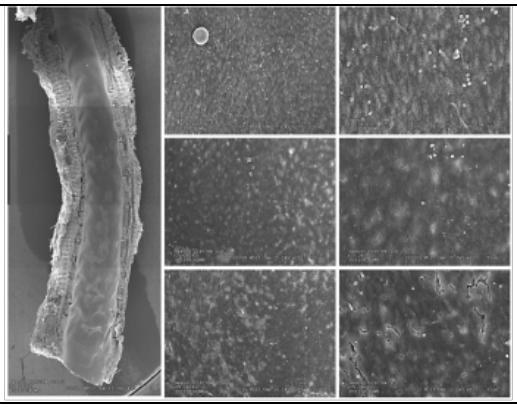
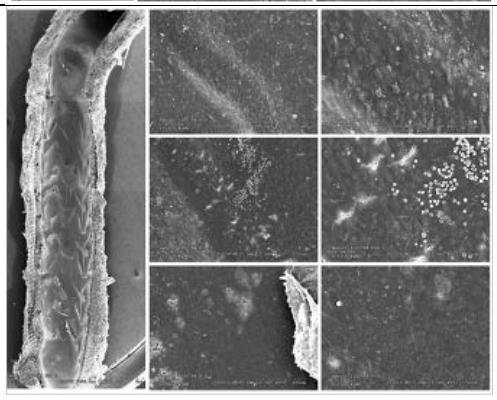
Preclinical studies conducted with Absorb and Xience V demonstrate comparable safety and vascular healing with these two devices. As described in **Section 3.3**, Absorb safety has been evaluated extensively in preclinical studies using the porcine coronary artery model with follow-ups from 3 days through 48 months. Shortly after implantation (3 days; **Figure 4.5.1-8**), struts of both Absorb and Xience, which was used as a control, demonstrated minimal to mild coverage with fibrin. Thereafter, near complete (> 90%; 1 month) to complete (> 1 month) endothelialization of the implanted arteries was demonstrated by scanning electron microscopy (SEM) analysis (**Figure 4.5.1-9**). From 1 to 48 months, arteries implanted with Absorb and Xience were widely patent, and both implants were incorporated in a benign, smooth muscle cell-rich neointima (**Figure 4.5.1-10**). At none of the follow-up time points from 3 days to 48 months was there evidence of thrombosis or device-related thrombo-embolization as based on the thorough evaluation of downstream myocardium and peripheral organs.



Top: Representative photomicrographs of porcine coronary arteries 3-days post-implantation with Absorb and Xience. Movat's pentachrome, 2x objective.

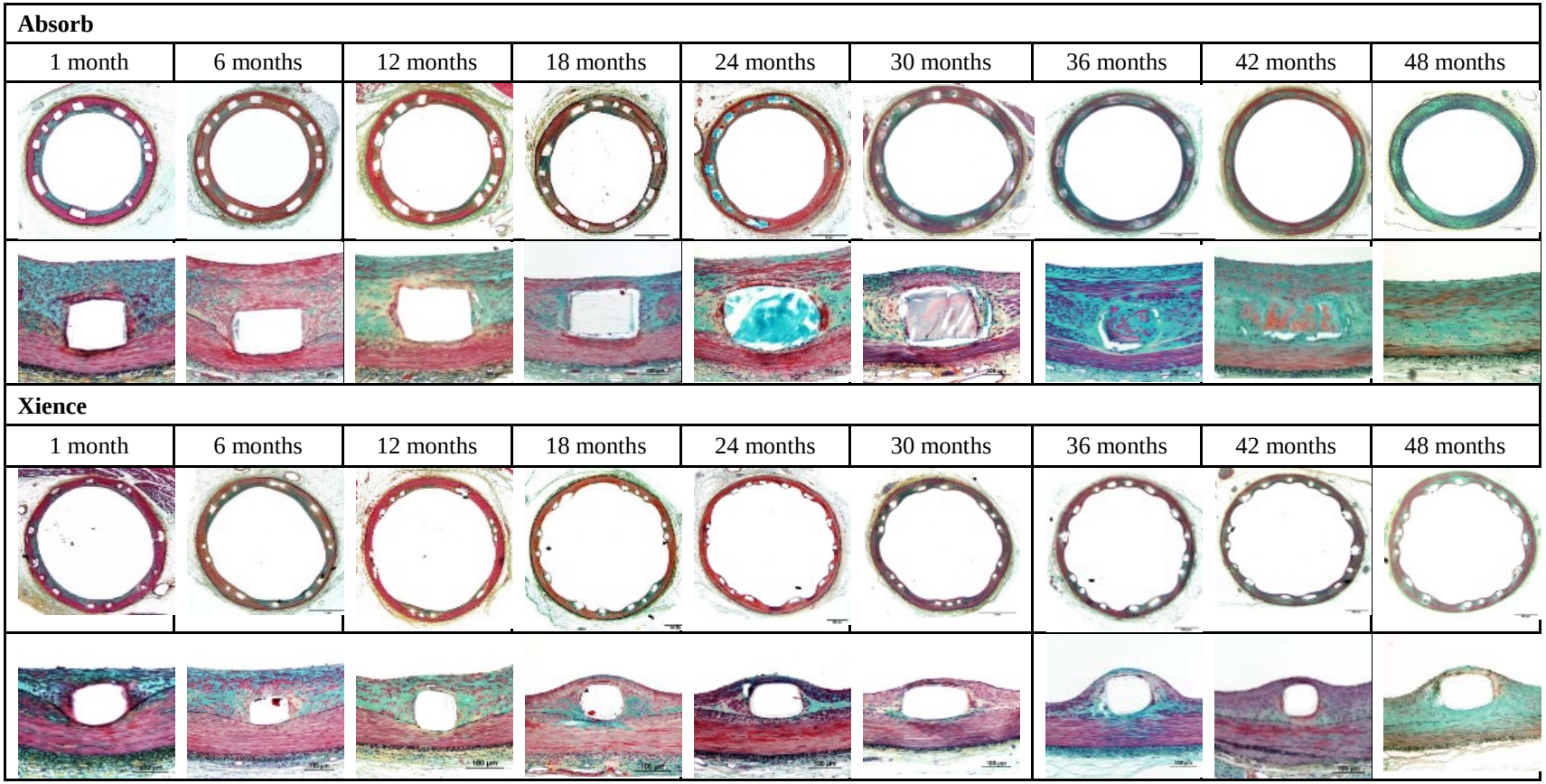
Bottom: Both devices show comparable and low amounts of fibrin overlying struts. Data previously reviewed by FDA but re-presented here with normalization to total strut surface area (number of struts per section and strut surface area). Data presented as mean ± SD. Absorb N = 12, Xience N = 7.

Figure 4.5.1-8 Three-Day Preclinical Safety Assessment of Absorb and Xience

Time Point	Absorb	Xience
1 month		
3 months		
6 months		

Note: Luminal surfaces of longitudinally sectioned porcine coronary arteries show confluent coverage by endothelium.

Figure 4.5.1-9 En Face SEM of Porcine Coronary Arteries at 1, 3, and 6 Months Post-Implantation with Absorb (left) and Xience (right)



Note: Movat's Pentachrome, 20x and 20x objectives

Figure 4.5.1-10 Representative Photomicrographs of Porcine Coronary Arteries Implanted with Absorb and Xience from 1 to 48 Months

4.5.2 Restoration and Resorption Phases

The *restoration phase* (from 6 months to approximately 18 months) represents the transition of Absorb from a vehicle for drug delivery and vessel support to a passive implant. As degradation continues through this phase, substantial reductions in vessel support and scaffold continuity occur, and the constriction and dilation of the vessel cease to be inhibited. This decline in scaffolding effectively enables the return of vessel vasomotion and pulsatility and allows for late lumen enlargement to occur through adaptive remodeling.

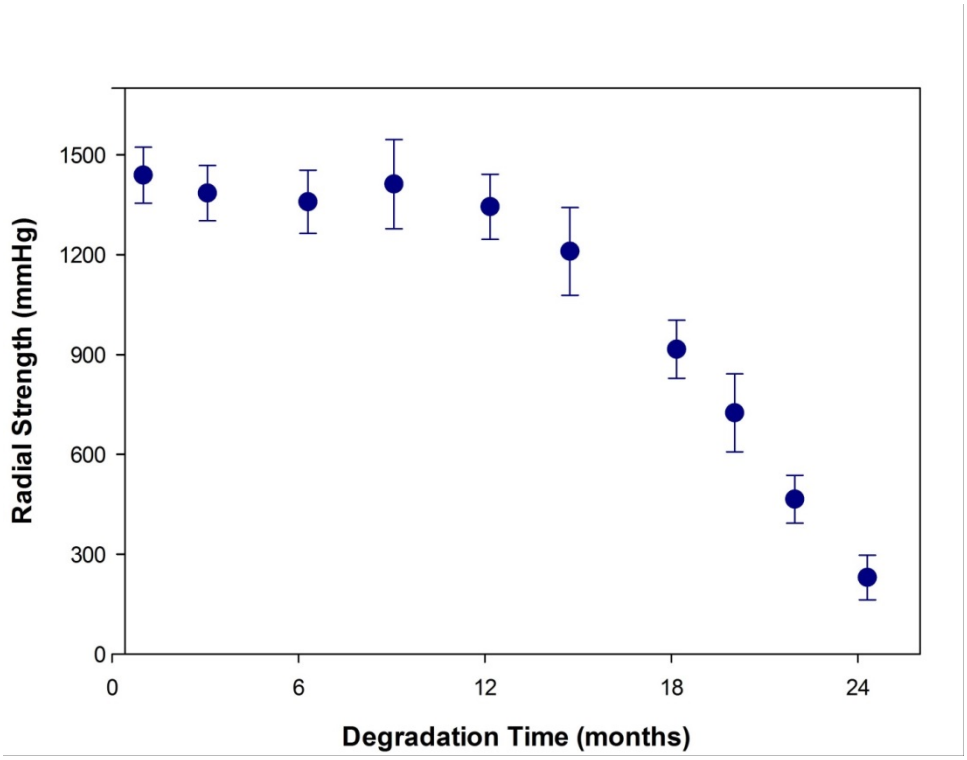
By the beginning of the *resorption phase* (approximately 18 months after implantation), Absorb has lost structural integrity (support and continuity) and is a functionally inert implant. During this phase the PLA continues to benignly resorb, with resorption being complete by approximately 36 months. The positive vessel adaptations initiated in the restoration phase continue to progress during the resorption phase to inevitably result in a vessel with more natural vasomotion and functional flow area.

As shown in **Figure 4.4-2**, Absorb undergoes bulk degradation rather than surface degradation. During the *revascularization* phase (implant to 6 months), the scaffold is non-porous, and there is only shortening of the polymer chains (decline in molecular weight) without loss of the polymer mass. By the end of this revascularization phase, clinical and preclinical studies have demonstrated complete neointimal coverage of the struts (**Section 6.4.2**). In the *restoration phase* (6 to approximately 18 months), polymer chains continue to shorten, resulting in loss of Absorb structural integrity. Struts remain covered in neointima which precludes possible embolization of the degrading scaffold. Finally, in the *resorption phase* (18 months and beyond), there is increasing porosity of the scaffold with concomitant adsorption of proteins into the porous strut, ensuring that particulates are not shed during this final resorption phase and providing a matrix for cellularization. Abbott Vascular has conducted extensive preclinical studies through the full course of degradation, and there has been no evidence of fragment generation or embolization either prior to or following tissue coverage.

The sections that follow detail the performance goals for the restoration and resorption phases and provide evidence of how Absorb has met these goals.

Gradual Loss of Radial Strength

The Absorb scaffold radial strength begins to gradually decline after 6 to 9 months. This gradual decline is visible in the radial strength data from an *in vitro* degradation study of Absorb shown in **Figure 4.5.2-1**, below.



Note: Data presented are mean ± SD for Absorb 3.0 x 18 mm scaffold. N = 6 per time point.

Figure 4.5.2-1 Absorb Radial Strength as a Function of Degradation Time

Biocompatibility throughout Resorption

Abbott Vascular has conducted comprehensive biocompatibility testing on Absorb following ISO10993 guidance and draft FDA biocompatibility guidance. Absorb passed all tests based on pre-determined acceptance criteria. In addition, Abbott Vascular has performed chemical / physical characterization over the life-cycle of the product and a toxicological assessment of all possible components in and released from the scaffold during the course of degradation. This comprehensive biocompatibility package demonstrated biocompatibility of Absorb product over the full life of the product.

Abbott Vascular has also evaluated Absorb in porcine coronary arteries throughout the scaffold's full course of degradation. The Absorb scaffold begins to lose mass significantly after 18 months, with complete mass loss occurring by approximately 36 months. At each time point evaluated, and specifically over the course of the most rapid mass loss from 18 to 36 months, all preclinical safety criteria were met, including systemic, angiographic, and histological end points. This includes the mean inflammation scores which were generally minimal to mild at all time points to 48 months. As illustrated previously in **Figure 4.5.1-10**, the vascular responses to both Absorb and Xience were benign, with arteries retaining normal anatomy with widely patent lumens and mild neointimal proliferation to cover struts. Arterial necrosis, medial loss, or adventitial fibrosis were not observed at any time point.

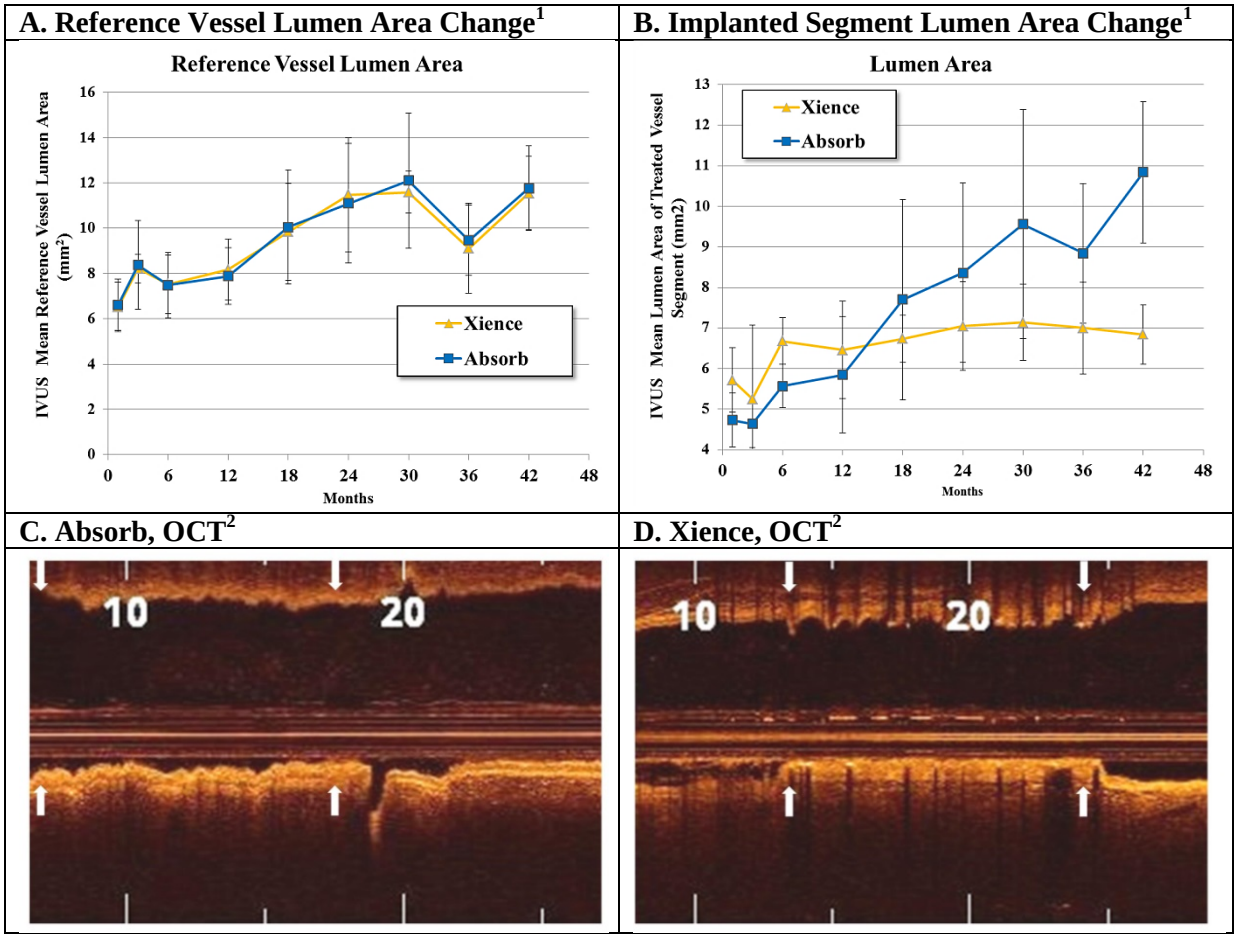
Potential Benefits of Bioresorption

Preclinical studies conducted with Absorb have demonstrated lumen enlargement via expansive vascular remodeling [46, 47], normalization of in-scaffold lumen area with the reference vessel [46], and restoration of both in-segment pulsatility [46], and vasomotion [35]. Each of these aspects are illustrated in **Figure 4.5.2-2**.

Late Lumen Enlargement

From 12 to 42 months, there is a progressive increase in the reference vessel lumen area [2] of both Absorb and Xience implanted arteries (**Figure 4.5.2-2A**), though in the implanted region, a comparable trend of lumen area increase is only appreciable in Absorb-implanted arteries (**Figure 4.5.2-2B**). Effectively this in-scaffold lumen area increase yields a normalization of the in-scaffold lumen area in Absorb-implanted arteries, which can be readily appreciated in longitudinal OCT pullbacks (**Figure 4.5.2-2C, D**). A smooth transition from native vessel to the implanted region is visible in Absorb-implanted arteries (**Figure 4.5.2-2C**). In contrast, a step-effect between the distal and proximal reference vessel and the stented segment is apparent in arteries implanted with Xience (**Figure 4.5.2-2D**).

[2] Reference vessel lumen area is defined as the lumen area of the naïve vessel just proximal to the implanted segment.

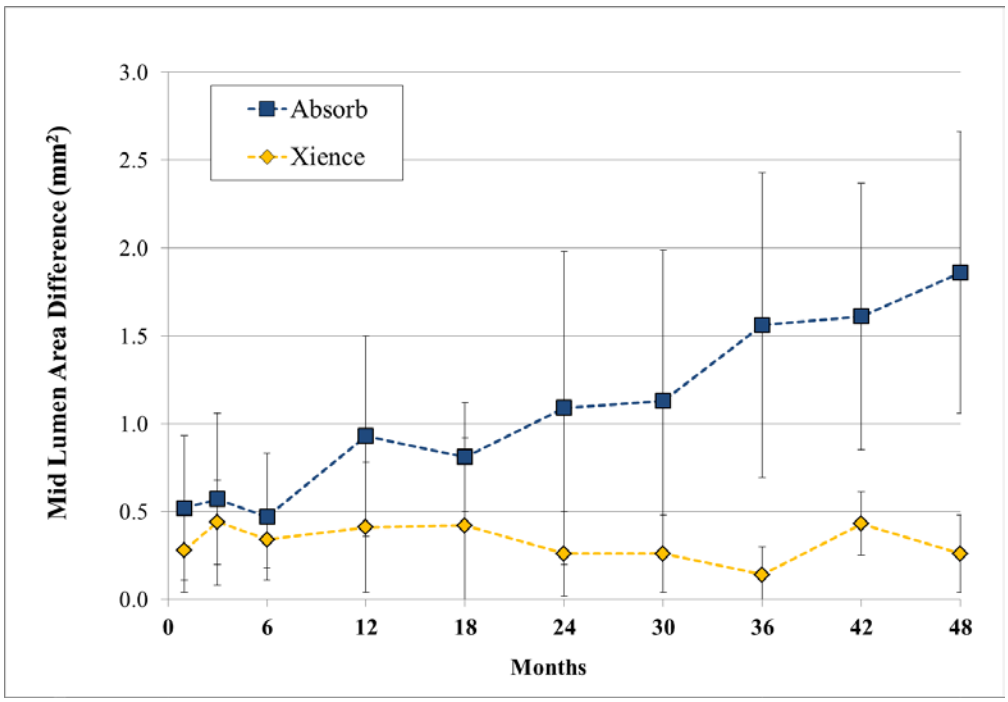


1 Mean (± SD), N = 9 - 18 Absorb, N = 6 - 11 Xience.
2 Longitudinal OCT of Absorb and Xience implanted porcine coronary arteries 42 months post-implantation. Arrows designate distal (left) and proximal (right) ends of the scaffold (C) and stent (D).

Figure 4.5.2-2 Late Lumen Gain (A, B) and Normalization of In-Segment Lumen Area (C, D) in Absorb Implanted Arteries

Restoration of Pulsatility

By determining the difference in lumen area between end-diastole and end-systole, the pulsatility of an artery can be determined. In Absorb-implanted arteries, there is a progressive increase in arterial pulsatility beginning around 6 to 12 months (**Figure 4.5.2-3**). Conversely, Xience-implanted arteries show only limited pulsatility from 1 to 48 months, consistent with the permanent caging of the artery.



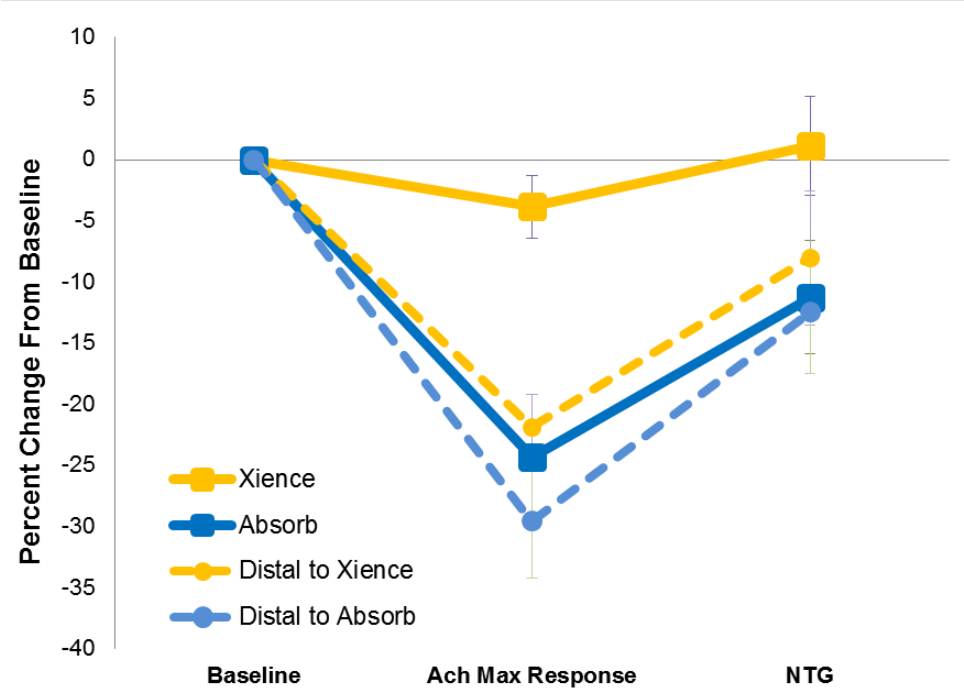
Note: N = 9 - 18 Absorb; N = 6 - 11 Xience. Mid lumen area difference = end-diastolic mid lumen area - end systolic mid lumen area. Data presented as mean ± SD. Each animal received at least one Xience and either one or two Absorb as the anatomy allowed.

Figure 4.5.2-3 Restoration of Pulsatility Observed in Absorb-Implanted Porcine Coronary Arteries: 1 to 48 months

Restoration of Vasomotion

An *in vivo* study conducted to evaluate the restoration of vasomotion has shown that at one and two years post-implant, Absorb-implanted arteries respond with comparable vasoconstriction to acetylcholine (Ach) and vasodilation to nitroglycerin (NTG) as the distal, untreated vessel segment (**Figure 4.5.2-4**). Arteries implanted with Xience had little response to these vasoactive agents [35].

Collectively these potential benefits are coordinated with the scaffold's performance profile (refer to **Figure 4.5-1**) which includes a projected loss of scaffold support around 12 months post-implant. These benefits of Absorb have been obtained while maintaining an *in vivo* safety profile comparable to that of Xience [47].



Note: Mean (± SD), N = 8 Absorb and distal untreated segments; N = 7 Xience and untreated distal segments

Figure 4.5.2-4 Angiographic Restoration of Vasomotion in Absorb-Implanted Porcine Coronary Arteries: 12 months [35]

These preclinical indicators, while obtained in non-diseased coronary arteries, have predicted the clinical safety and the same technology-unique outcomes of lumen gain and a restoration of vasomotion reported in ABSORB clinical trials [48-51].

The ABSORB Cohort B trial was a first in man study of 101 subjects designed with imaging modalities to study late lumen enlargement and vasomotor function in humans following Absorb implantation. In line with preclinical studies, late lumen enlargement and restoration of vasomotor function were observed in the ABSORB Cohort B study. In addition, data from OCT imaging at 5 years showed a healed vessel with absence of visible struts, consistent with complete bioresorption and integration into the arterial wall.

The imaging analyses performed in the ABSORB Cohort B trial demonstrated that porcine data could be replicated in human: IVUS data demonstrated late lumen gain, OCT interrogation illustrated integration of resorbed Absorb struts by 5 years, and vasomotor function analyses by injection of nitroglycerine demonstrated that the treated segment of the vessel was able to respond to physiologic stimuli and expand. Clinical outcomes for the ABSORB Cohort B trial as well as detailed imaging and vasomotor function data are provided **Section 6.0**.

5.0 Pivotal Clinical Trial - ABSORB III Randomized Controlled Trial

5.1 ABSORB III Methods

Key Points:

- The ABSORB III Randomized Controlled Trial (RCT) (ABSORB III) evaluates the safety and effectiveness of Absorb Bioresorbable Vascular Scaffold System (Absorb).
    - 2:1 comparison of Absorb to Xience
- The XIENCE control used in the study was intentionally selected since it is one of the most safe and effective FDA approved DES. Several large scale meta-analysis have demonstrated that Xience:
    - has the lowest rate of definite ST, mortality and MI rates compared to BMS and other DES
    - is the most efficacious, demonstrated by lower short-term and long-term risks of TVR and TLR compared to BMS and DES
- According to FDA guidance, a non-inferiority margin of 4.5% was selected for the primary endpoint, representing 50% of a conservative treatment effect estimate of

The ABSORB III Randomized Controlled Trial (RCT) (ABSORB III) evaluates the safety and effectiveness of Absorb Bioresorbable Vascular Scaffold (BVS) System (Absorb). Absorb is compared to the control device, the commercially available Xience V, Xience PRIME, Xience Xpedition, Xience Alpine, Xience Pro (outside of the US only), and Xience Pro^{X} (outside of the US only). Hereinafter, the control devices will be called “Xience”.

5.1.1 ABSORB III Trial Design

An overview of the ABSORB III trial design is depicted graphically in **Figure 5.1.1-1**. The ABSORB III trial was planned to register approximately 2262 subjects, comprised of up to 50 subjects in a non-randomized lead-in group, approximately 2000 randomized (2:1 Absorb : Xience) subjects in the primary analysis group, approximately 200 subjects in a randomized imaging cohort (2:1 Absorb : Xience), and 12 subjects in a non-randomized PK sub-study. The primary analysis group primary and secondary endpoint results and conclusions are found in **Section 5.2** and **Section 5.3**, while the pharmacokinetics sub-study results are found in **Section 5.4**. A summary of the Lead-In Group trial design and key outcomes can be found in **Appendix 3**.

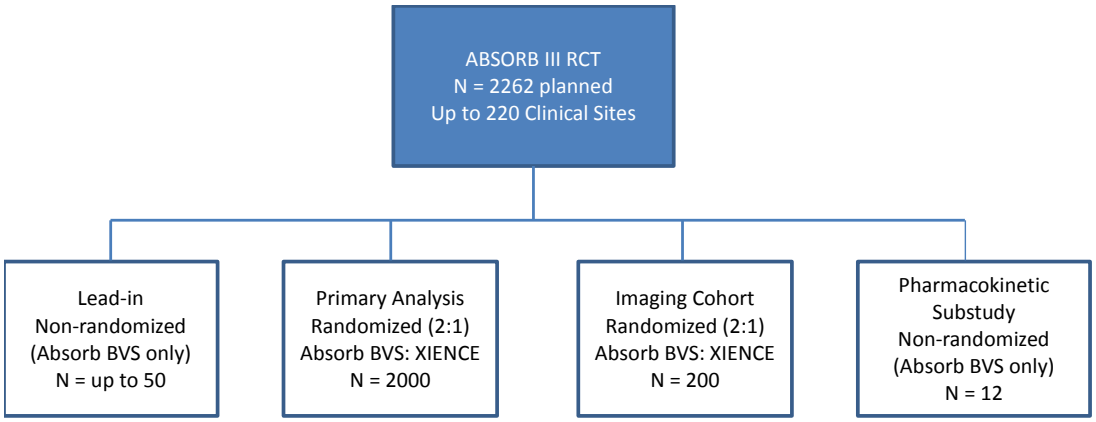


Figure 5.1.1-1 ABSORB III Overall Design

As mentioned above, the Xience DES is the comparator to Absorb in the ABSORB III trial, and perspective must be given on the selection of Xience as comparator. In several meta-analyses published in the past 3 years, Xience has demonstrated the best safety and effectiveness profile as compared to BMS or other DES. In fact, Xience emerges as the best-in-class among all currently available DES. In a meta-analysis including 49 trials and 50,844 subjects [17], Xience had the lowest rate of definite stent thrombosis compared to BMS, and other DES, at 1-year and 2-year post-implantation (**Figure 5.1.1-2**). In another meta-analysis, comparing several DES (EES, SES, PES and ZES) with each other and against BMS, Xience was again shown to be the safest DES based on 1-year ST and MI rates [3]. In the longer term, Xience's excellent safety profile is maintained. Xience was associated with lower rates of mortality, MI and ST as compared to BMS or other DES, in a meta-analysis of 51 trials, including a total of 52,158 randomized subjects with follow-up of 3 years or more [4]. Not only is Xience the safest stent, but it is also the most efficacious as demonstrated by lower short-term and long-term risks of TVR and TLR as compared to BMS and other DES [3, 17]. Therefore in the ABSORB III trial, the evaluation of the 1 year safety and effectiveness of Absorb is compared to one of the best DES within the PCI standard of care.

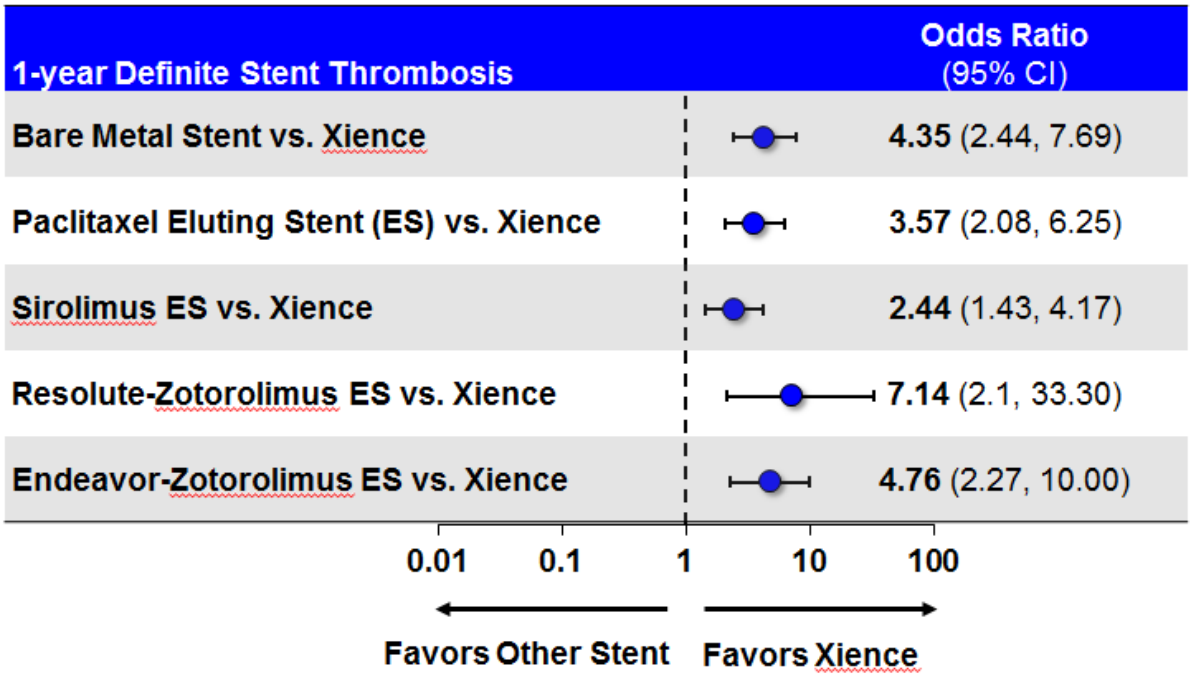


Figure 5.1.1-2 Stent Thrombosis Network Meta-Analysis (49 RCTs and 50,844 subjects) [17]

The lead-in group was a non-randomized group to evaluate the applicability and transferability of the didactic Absorb BVS physician training plan to United States (US) clinical practice in up to 50 subjects. There were only 24 subjects enrolled. Details on the Lead-in baseline characteristics and follow-up results through 2 years are included in **Appendix 3**. The imaging cohort is a randomized 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. There have been 186 subjects who have completed enrollment in the imaging study; they are yet to reach the 3 year primary endpoint. The lead-in group and imaging cohort did not contribute to the primary endpoint analysis and are not required as part of the assessment of the device for approval at 1 year.

Subject Enrollment

A total of 2008 subjects were randomized into the ABSORB III trial, with 1-year follow-up completed in 1,989 subjects (99.1%) (**Figure 5.2.1-2**). Subjects who consent to participation in ABSORB III and undergo screening are drawn from the interventional cardiology population and have a wide range of disease presentation and severity, ranging from no flow limiting lesions to highly complex lesions. The large number of angiographic exclusions in ABSORB III is based on eligibility criteria which are consistent with a non-complex patient population. Further details on the subject enrollment and screening can be found in **Figures 5.2.1-1** to **5.2.1-3**.

Study Blinding

ABSORB III is a single-blinded clinical trial. Subjects were blinded to their treatment assignment, and the study site personnel were trained not to disclose the treatment assignment to the subject. The physician performing the index procedure was not blinded to the assigned treatment. For clinical follow-up, a different physician (or designee) than the one who implanted the device(s) conducts visits in order to maintain subject blinding.

The angiographic core laboratory is responsible for reviewing all available follow-up coronary angiograms for registered subjects, to determine if a revascularization was performed by PCI, and if so, whether or not the revascularization was related to the target lesion, target vessel or non-target vessel. The angiographic core laboratory cannot be blinded to the device received. The Clinical Events Committee (CEC) is responsible for adjudicating specified clinical endpoints based on the criteria used for the categorization of clinical events in the trial. The Clinical Events Committee (CEC) is blinded to the randomization assignments. The Data Safety Monitoring Board (DSMB) is also be blinded to the subject's randomization. Independent statisticians generate blinded tables for review by the DSMB. The DSMB may request unblinded data if a safety signal is observed.

5.1.2 Primary Endpoint

As required per FDA guidelines, the ABSORB III trial is powered based on the primary endpoint of target lesion failure (TLF) at 1-year. TLF is defined as a per-subject hierarchical count of cardiac death, target vessel Q-wave or non-Q-wave MI (per protocol-defined MI definition, as defined in **Appendix 1**, or ischemia-driven target lesion revascularization (ID-TLR). The primary endpoint was tested on the primary analysis group in which 2008 subjects were enrolled. As will be further detailed in **Section 5.2.1**, the ITT population in which the analysis was performed, included a total of 1990 subjects.

5.1.3 Number of Clinical Sites and Investigator Information

There were a total of 193 enrolling sites in the ABSORB III trial, of which 191 were located in the US and 2 were located in Australia. The list of participating investigators and enrollment in the primary analysis group by site can be found in **Appendix 2**.

5.1.4 Subject Selection and Exclusion Criteria

Subjects registered into this clinical investigation were derived from the general interventional cardiology population, having a maximum of two *de novo* native coronary artery lesions in separate epicardial vessels, who meet all eligibility criteria, and have provided written informed consent. Key eligibility criteria are described below. Complete eligibility criteria can be found in **Appendix 1**.

Key General Inclusion Criteria:

- Subject must be at least 18 years of age.
- Subject must have evidence of myocardial ischemia (e.g., stable, unstable angina, post-infarct angina or silent ischemia) suitable for elective PCI. To ensure that subjects with stable angina and silent ischemia met criteria of myocardial ischemia, they were required to have < 70% diameter stenosis must have objective signs of ischemia as determined by one of the following, echocardiogram, nuclear scan, ambulatory ECG or stress ECG). In the absence of noninvasive ischemia, FFR must be done and indicative of ischemia.
- Subject must be an acceptable candidate for coronary artery bypass graft (CABG) surgery.
- Subject agrees to not participate in any other investigational or invasive clinical study for a period of 1 year following the index procedure.

Key General Exclusion Criteria:

- Any surgery requiring general anesthesia or discontinuation of aspirin and/or an ADP antagonist is planned within 12 months after the procedure.
- Subject had an acute myocardial infarction (AMI: STEMI or NSTEMI) within 72 hours of the index procedure and both CK and CK-MB have not returned to within normal limits at the time of index procedure; or subject with stable angina or silent ischemia has CK-MB that is greater than normal limits at the time of the index procedure.
- Subject is currently experiencing clinical symptoms consistent with new onset AMI (STEMI or NSTEMI), such as nitrate-unresponsive prolonged chest pain with ischemic ECG changes.
- Subject has a cardiac arrhythmia as identified at the time of screening for which at least one of the following criteria is met:
    i. Subject requires coumadin or any other agent for chronic oral anticoagulation
    ii. Subject is likely to become hemodynamically unstable due to their arrhythmia
    iii. Subject has poor survival prognosis due to their arrhythmia
- Subject has a left ventricular ejection fraction (LVEF) < 30% assessed by any quantitative method, including but not limited to echocardiography, MRI, Multiple-Gated Acquisition (MUGA) scan, contrast left ventriculography, PET scan, etc. LVEF may be obtained within 6 months prior to the procedure for subjects with stable CAD. For subjects presenting with ACS, LVEF must be assessed during the index hospitalization (which may include during the index procedure by contrast left ventriculography) but prior to randomization in order to confirm the subject's eligibility.
- Subject has undergone prior PCI within the target vessel during the last 12 months. Prior PCI within the non-target vessel or any peripheral intervention is acceptable if

performed anytime >30 days before the index procedure, or between 24 hours and 30 days before the index procedure if successful and uncomplicated.
- Subject requires future staged PCI either in target or non-target vessels or subject requires future peripheral interventions < 30 days after the index procedure.
- Subject has renal insufficiency as defined as an estimated GFR < 30 ml/min/1.73m^2 or dialysis at the time of screening.

Key Angiographic Inclusion Criteria:

- One or two *de novo* target lesions:
    i. If there is one target lesion, a second non-target lesion may be treated but the non-target lesion must be present in a different epicardial vessel, and must be treated first with a successful, uncomplicated result prior to randomization of the target lesion.
    ii. If two target lesions are present, they must be present in different epicardial vessels and both must satisfy the angiographic eligibility criteria.
    iii. The definition of epicardial vessels means the LAD, LCX and RCA and their branches. Thus, the subject must not have lesions requiring treatment in e.g. both the LAD and a diagonal branch.
- Target lesion(s) must be located in a native coronary artery with a visually estimated or quantitatively assessed %DS of ≥ 50% and < 100% with a TIMI flow of ≥1 and one of the following: stenosis ≥ 70%, an abnormal functional test (e.g. fractional flow reserve, stress test), unstable angina or post-infarct angina.
    i. Lesion(s) must be located in a native coronary artery with RVD by visual estimation of ≥ 2.5 mm and ≤ 3.75 mm.
    ii. Lesion(s) must be located in a native coronary artery with length by visual estimation of ≤ 24 mm.

Key Angiographic Exclusion Criteria

All exclusion criteria apply to the target lesion(s) or target vessel(s).

- Lesion which prevents successful balloon pre-dilatation, defined as full balloon expansion with the following outcomes:
    i. Residual %DS is a maximum of < 40% (per visual estimation), ≤ 20% is strongly recommended.
    ii. TIMI Grade-3 flow (per visual estimation).
    iii. No angiographic complications (e.g. distal embolization, side branch closure).
    iv. No dissections NHLBI grade D-F.
    v. No chest pain lasting > 5 minutes.
    vi. No ST depression or elevation lasting > 5 minutes
- Lesion is located in left main.
- Aorto-ostial RCA lesion (within 3 mm of the ostium).

- Lesion located within 3 mm of the origin of the LAD or LCX.
- Lesion involving a bifurcation with a:
    i. side branch ≥ 2 mm in diameter, or
    ii. side branch with either an ostial or non-ostial lesion with diameter stenosis > 50%, or
    iii. side branch requiring dilatation.
- Vessel contains thrombus as indicated in the angiographic images or by IVUS or
- Target lesion located within an arterial or saphenous vein graft or distal to any arterial or saphenous vein graft.

5.1.5 Analysis Populations

Intention to Treat (ITT) Population:

The ITT population included all subjects registered in the study at the point of randomization, regardless of the treatment actually received (N = 2008). Subjects were analyzed in the treatment group to which they were randomized.

Per-Treatment-Evaluable Population (PTE):

The PTE population was comprised of subjects who received only study device(s) (Absorb or Xience) at the target lesion, but excluded those with specific protocol deviations to the eligibility criteria and treatment strategy. Analyses based on the PTE population will be "as treated". Subjects will be included in the treatment group corresponding to the study device actually received. Complete details of the PTE criteria can be found in **Appendix 1**.

As-Treated (AT) Population:

Treatment group assignment in the AT population was based on the treatment (Absorb or Xience) actually received (N = 1987). Subjects who received both Absorb and Xience in separate target lesions were included in the treatment group they were randomized to. Subjects who received both Absorb and Xience in the same target lesion (N=10) and those who received no study device (N = 11) were excluded from the AT population.

For the presentation of data, primary analysis and powered secondary endpoints will be presented in all three populations. All additional analysis will be presented for ITT being the primary analysis and AT reflecting the treatment (Absorb or Xience) actually received in the enrolled population.

5.1.6 Statistical Overview

The primary endpoint of TLF at 1 year is evaluated using the difference in event rates in the intent-to-treat (ITT) population. The ABSORB III results will be presented in the ITT population as well as the AT 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 (NI) margin for the primary endpoint.

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.

The sample size calculation for the primary endpoint of TLF at 1-year follow-up is based on the following assumptions:

- One-sided non-inferiority test
- $\alpha = 0.025$
- Randomization ratio is 2 (Absorb arm) : 1 (Xience arm)
- The true TLF rate is assumed to be 7.0% for both the Absorb arm and the Xience arm
- Non-inferiority margin (delta) of 4.5%

Based on the above assumptions, a total of 1,900 subjects (1,267 for the Absorb arm and 633 for the Xience arm) would provide approximately 96% power. Assuming a 5% dropout rate at 1 year (which is a common assumption for contemporary trials), approximately 2,000 subjects were to be enrolled.

5.1.7 Justification of the True Rate Assumption and the NI Margin for the Primary Endpoint

The true rate assumption of 7% for 1-year TLF for both the Absorb arm and the Xience arm in ABSORB III was based on the data of similar Xience patient population (N = 2051) from the SPIRIT IV trial. The original TV-MI component of TLF in SPIRIT IV was based on WHO definition and ARC definition. Because ABSORB III used a different MI definition based on CK-MB elevation, the TLF rate in SPIRIT IV was re-derived using patient-level CK-MB data. The 1-year TLF rate in SPIRIT IV per the ABSORB III MI definition was calculated to be 6.1% with an upper one-sided 95% confidence limit of 7%. In order to account for the variation associated with different trials (e.g., missing data, difference in CK-MB collection schedule, etc.), 7% was selected to be the true rate assumption.

The NI margin of 4.5% for the primary endpoint was selected following FDA's guidance on non-inferiority clinical trials [2], and agreed upon with the FDA. This involved two steps; first, the treatment effect of Xience over a putative placebo, bare-metal stent (BMS) was estimated based on meta-analysis of historical trials. Second, the NI margin was selected as

50% of the treatment effect estimate in order to preserve at least 50% of the treatment effect of Xience in ABSORB III.

Because there was no historical trial comparing Xience and BMS directly in the patient population similar to ABSORB III, an indirect approach was taken by first comparing Xience against TAXUS/CYPHER (1st generation DES) and TAXUS/CYHPER against BMS, separately, then combining the two treatment effect estimates as the estimate for Xience over BMS. Through literature review, four large US and European randomized controlled trials (RCTs) were included in the meta-analysis. The results were listed in **Tables 5.1.7-1a** and **5.1.7-1b**, below.

Table 5.1.7-1a Meta-Analysis of Historical RCTs comparing 1st Gen DES and BMS

Trial Name	1st Gen DES	BMS	Treatment Effect Estimate* Risk Difference ± Standard Error [90% CI]
SIRIUS [52]	8.3% (44/533)	22.3% (117/525)	11.6% ± 0.0231 [7.8%, 15.4%]
TAXUS IV [53]	10.0% (64/639)	19.4% (123/633)	

* Random effect meta-analysis (Dersimonian and Laird method) [54]
Note: Based on event rates of MACE, which is a composite of cardiac death, MI, and TLR.

Table 5.1.7-1b Meta-Analysis of Historical RCTs comparing Xience and 1st Gen DES

Trial Name	Xience	1st Gen DES	Treatment Effect Estimate* Risk Difference ± Standard Error [90% CI]
SPIRIT IV [8]	4.2% (102/2416)	6.9% (82/1195)	2.5% ± 0.0077 [1.2%, 3.7%]
ISAR TEST IV [55]	13.6% (89/652)	15.2% (99/652)	

* Random effect meta-analysis (Dersimonian and Laird method) [54]
Note: Based on event rates of MACE, which is a composite of cardiac death, MI, and TLR.

According to FDA's guidance, the lower bound of the confidence interval, 7.8% for 1st Gen DES vs BMS and 1.2% for Xience vs 1st Gen DES, was taken as a conservative treatment effect estimate for each comparison. By combining the two estimates, the treatment effect of Xience over BMS was estimated to be 9%. The NI margin was selected to be 4.5% in order to preserve at least 50% of the treatment effect estimate of Xience over BMS.

Two sensitivity analyses are provided in order to support the selection of 9% as the treatment effect estimate of Xience over BMS.

Sensitivity Analysis 1:

Instead of taking the lower one-sided 95% confidence bound of each comparison as conservative treatment effect estimates and then combining them to get the overall treatment effect estimate, a statistically more robust way would be to directly add the two point

estimates of the treatment effect and then calculate the corresponding lower one-sided 95% confidence bound.

Based on the results of the meta-analysis in **Tables 5.1.7-1a** and **5.1.7-1b** above, the point estimates of the treatment effect of Xience over BMS can be estimated by combining the point estimates of the treatment effect of Xience over 1st Gen DES and 1st Gen DES over BMS, which was calculated to be 14.1% (11.6%+2.5%), with a standard error of 0.0243 ($\sqrt{0.0231^2 + 0.0077^2}$), and a corresponding two-sided 90% confidence interval of [10.1%, 18.1%]. By taking the lower bound of the confidence interval, the treatment effect estimate of Xience over BMS would be 10.1%. This supports the conservativeness of the treatment effect estimate of 9%.

Sensitivity Analysis 2:

Based on extensive literature review, there were a total of 23 trials comparing Xience vs TAXUS/CYPHER (1st generation DES) or TAXUS/CYPHER vs BMS, of which 10 were conducted on a specific sub-population such as AMI, diabetic, etc. Therefore an additional meta-analysis was conducted by including 13 RCTs and the results were shown in **Tables 5.1.7-2a** and **5.1.7-2b**, below.

Table 5.1.7-2a Meta-Analysis of Historical RCTs comparing 1st Gen DES and BMS

Trial Name	1st Gen DES	BMS	Treatment Effect Estimate* Risk Difference ± Standard Error [90% CI]
SIRIUS [52]	8.3% (44/533)	22.3% (117/525)	12.6% ± 0.0208 [9.2%, 16.1%]
TAXUS IV [53]	10.0% (64/639)	19.4% (123/633)	
RAVEL [56]	5.8% (7/120)	28.8% (34/118)	
TAXUS I [57]	3.3% (1/30)	10.0% (3/30)	
TAXUSII [58]	10.5% (28/268)	21.6% (58/268)	

* Random effect meta-analysis (Dersimonian and Laird method) [54]
Note: Based on event rates of DMR (death, MI, and revascularization), MACE (cardiac death, MI, and TLR), TVF (cardiac death, MI, and TVR), or TLF (cardiac death, TV-MI, and TLR) at 1 year.

Table 5.1.7-2b Meta-Analysis of Historical RCTs comparing Xience and BMS/ 1st Gen DES

Trial Name	Xience	BMS / 1st Gen DES	Treatment Effect Estimate* Risk Difference ± Standard Error [90% CI]
SPIRIT IV [8]	4.2% (102/2416)	6.9% (82/1195)	1.7% ± 0.006 [0.8%, 2.7%]
ISAR TEST IV [55]	13.6% (89/652)	15.2% (99/652)	
SPIRIT II [59]	2.7% (6/225)	9.3% (7/75)	
SPIRIT III [7]	6.0% (39/653)	10.3% (33/320)	
COMPARE [60]	6.2% (56/897)	9.1% (82/903)	
RESET [61]	6.1% (97/1597)	7.6% (122/1600)	
SORT OUT IV [62]	7.1% (99/1390)	7.6% (105/1384)	
EXCELLENT [63]	3.8% (40/1067)	3.1% (11/361)	

* Random effect meta-analysis (Dersimonian and Laird method) [54]

Note: Based on event rates of DMR (death, MI, and revascularization), MACE (cardiac death, MI, and TLR), TVF (cardiac death, MI, and TVR), TLF (cardiac death, TV-MI, and TLR), or the composite of death, MI, and TVR at 1 year, or the composite of cardiac death, MI, and definite ST at 18 months.

Based on the meta-analysis above, the point estimate of the treatment effect of Xience over BMS was calculated to be 14.3% (12.6% + 1.7%), with a standard error of 0.0216 ($\sqrt{0.0208^2 + 0.006^2}$), and a corresponding two-sided 90% confidence interval of [10.7%, 17.9%]. By taking the lower bound of the confidence interval, the treatment effect estimate of Xience over BMS would be 10.7%. This again suggests that the choice of 9% was reasonably conservative.

5.1.8 Secondary Endpoints

There were three pre-specified endpoints which tested the superiority of Absorb to Xience at 1 year.

- Angina, defined as the first adverse event resulting in the site diagnosis of angina. The analysis excludes angina following the index procedure through discharge, not to exceed a period of 7 days.
- All revascularizations, comprised of TLR, TVR excluding TLR, and non-TVR.
- Ischemia-driven target vessel revascularization (ID-TVR).

The above powered secondary endpoints were added to the protocol based on an initial signal of lower angina rates in Absorb compared to Xience, identified in two post-hoc retrospective non-powered analyses, the propensity matched analysis of ABSORB EXTEND versus SPIRIT IV (28.1% vs 16.0%, HR = 0.53 [0.39,0.74], p = 0.0001), and the ABSORB II randomized trials (14.5% vs 23.2%, p = 0.02). Additionally, in ABSORB II there was a signal of lower all revascularization rates in Absorb compared to Xience (3.6% vs 7.3%, p = 0.07). Based on this data, an assumption was made that less angina would be associated with less target vessel and all revascularization. Because it's not uncommon to find dramatic treatment effect in small studies [64], which were hypothesis generating, it is important to

further investigate these findings prospectively in a large randomized trial, such as ABSORB III. A valid scientific approach was taken in ABSORB III to determine whether Absorb's novel technology was associated with advantages to metallic DES in angina, all revascularization and ID-TVR at 1 year.

Other secondary endpoints include:

- Stent/scaffold thrombosis (per ARC definition), assessed based on timing (acute, sub-acute, late and very late) and evidence (definite and probable)
- Clinical Device Success (Lesion Basis)
  Successful delivery, deployment, and withdrawal at intended target lesion with final in-scaffold/stent residual stenosis of less than 30% by QCA
- Clinical Procedure Success (Subject Basis)
  - Final in-scaffold/stent residual stenosis of less than 30% by QCA
  - Successful delivery and deployment of at least one study scaffold/stent at intended target lesion
  - Successful withdrawal of delivery system for all target lesions without occurrence of cardiac death, target vessel MI or repeat TLR during hospital stay
- Death/All MI/All revascularization (DMR)
- Cardiac Death/All MI/ID-TLR/ID-TVR, non TL (Target Vessel Failure, TVF)
- Cardiac Death/All MI/ID-TLR (MACE)
- Cardiac Death/TV-MI/ID-TLR (TLF)

5.2 ABSORB III Results

Key Points:

- ABSORB III achieved its primary study objective, demonstrating non-inferiority in TLF at 1 year compared to Xience (**Table 5.2.2-1**). The design and results of the ABSORB III trial meet FDA's regulatory standard for approval of coronary DES.
- The TLF rate at 1 year was 7.8% in the Absorb arm and 6.1% in the XIENCE arm ($P_{non\text{-}inferiority}$ =0.007) in the ITT population.
- One-year results for safety endpoints such as death, myocardial infarction and device thrombosis are summarized in **Tables 5.2.2-13** and **5.2.2-14**. The observed rates were low overall with no statistical differences between the two device arms, demonstrating a reasonable assurance of safety.
- Absorb demonstrated reasonable assurance of effectiveness, with ID-TLR rates comparable to Xience. Absorb preserves the effectiveness of current-day metallic DES compared to prior PCI treatments.
- In addition to Absorb showing non-inferiority in the overall population, the outcomes in the patient population closely aligned with the label (2.5-3.75 mm) provide evidence that when Absorb is placed in the appropriately sized vessels the differences between the two arms are further reduced.

5.2.1 Summary of Trial Population and Procedural Information

Baseline Subject Characteristics and Risk Factors

From a total of 13,789 subjects screened for eligibility in ABSORB III, between March 22nd 2013 and April 3rd, 2014, 2008 subjects were randomized to Absorb (N = 1322) or Xience (N = 686) (**Figure 5.2.1-1**), comprising the Intent-to-Treat (ITT) population of the study.

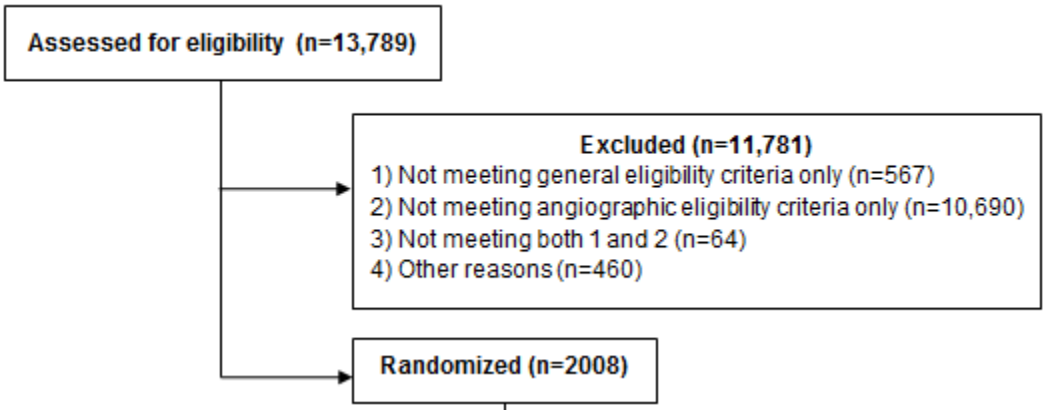
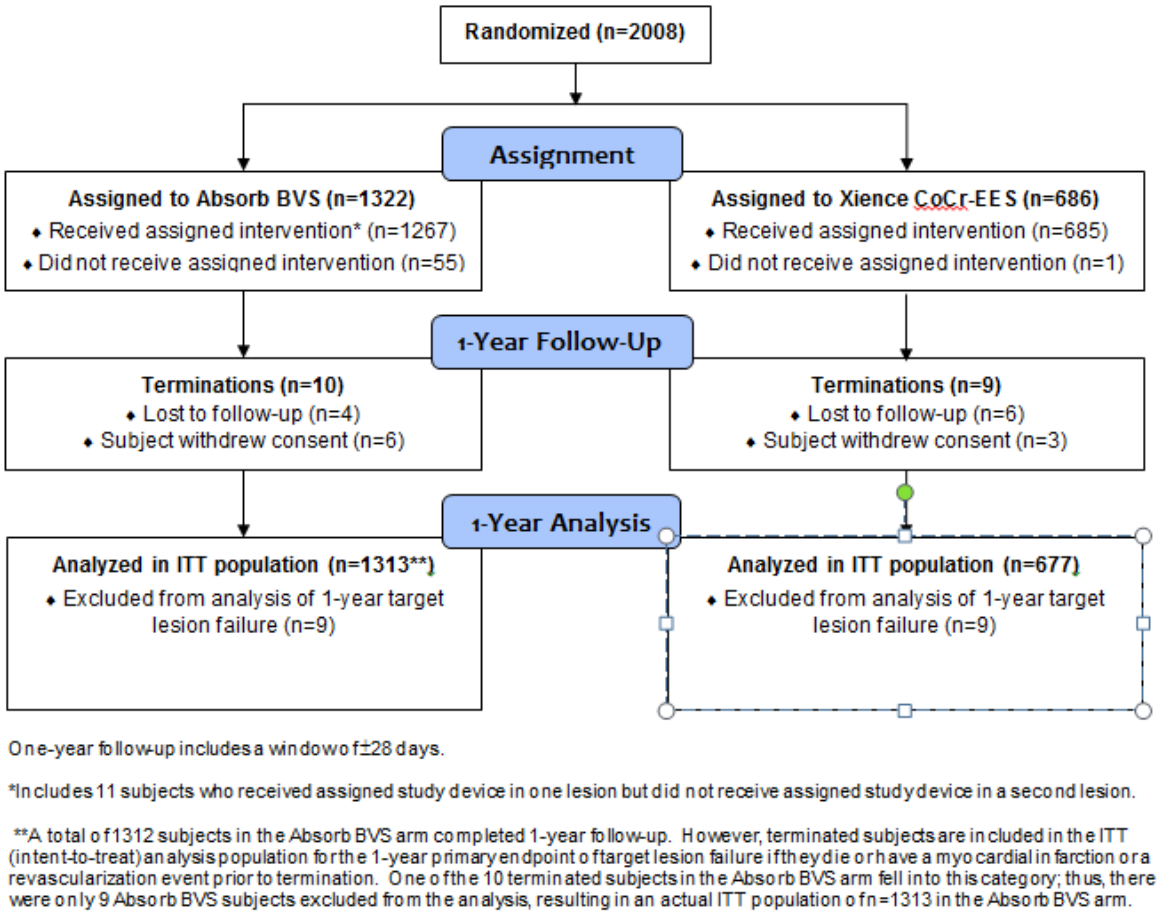


Figure 5.2.1-1 Subjects Eligible and Screened in ABSORB III

The subject flow and 1-year follow-up in the ITT population are depicted in **Figure 5.2.1-2**. One-year follow-up rates were 99.2% (1312/1322) in the Absorb arm and 98.7% (677/686) in the Xience arm. A subject in the Absorb arm who had withdrawn from the study before 1-year follow-up is included in the 1-year ITT analysis population because he had a death/myocardial infarction/revascularization (DMR) clinical event prior to termination. Thus, the number of ITT subjects analyzed were N = 1313 in the Absorb arm and N = 677 in the Xience arm.



One-year follow-up includes a window of ±28 days.

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

**A total of 1312 subjects in the Absorb BVS arm completed 1-year follow-up. However, terminated subjects are included in the ITT (intent-to-treat) analysis population for the 1-year primary endpoint of target lesion failure if they die or have a myocardial infarction or a revascularization event prior to termination. One of the 10 terminated subjects in the Absorb BVS arm fell into this category; thus, there were only 9 Absorb BVS subjects excluded from the analysis, resulting in an actual ITT population of n=1313 in the Absorb BVS arm.

Figure 5.2.1-2 Subject Flow and 1-Year Follow-Up in Intent-to-Treat Population

Figure 5.2.1-3 presents the subject flow from the ITT population to the PTE population. Out of the 1322 Absorb subjects and 686 Xience subjects enrolled, there were a total of 95 and 54 subjects respectively, removed from the PTE population due to deviations meeting the specified PTE exclusion criteria (**Appendix 1**). A majority of the patients excluded in both device arms were due to deviations associated with the treatment strategy. There were also 47 crossovers from the Absorb arm to the Xience arm resulting in a PTE population of 1180 for the Absorb arm and 679 for the Xience arm. The final 1 year follow-up and1 year analysis of the PTE population included 1174 subjects in the Absorb arm and 670 subjects in the Xience arm due to 6 and 9 subjects in the Absorb and Xience arms, respectively, being lost to follow-up.

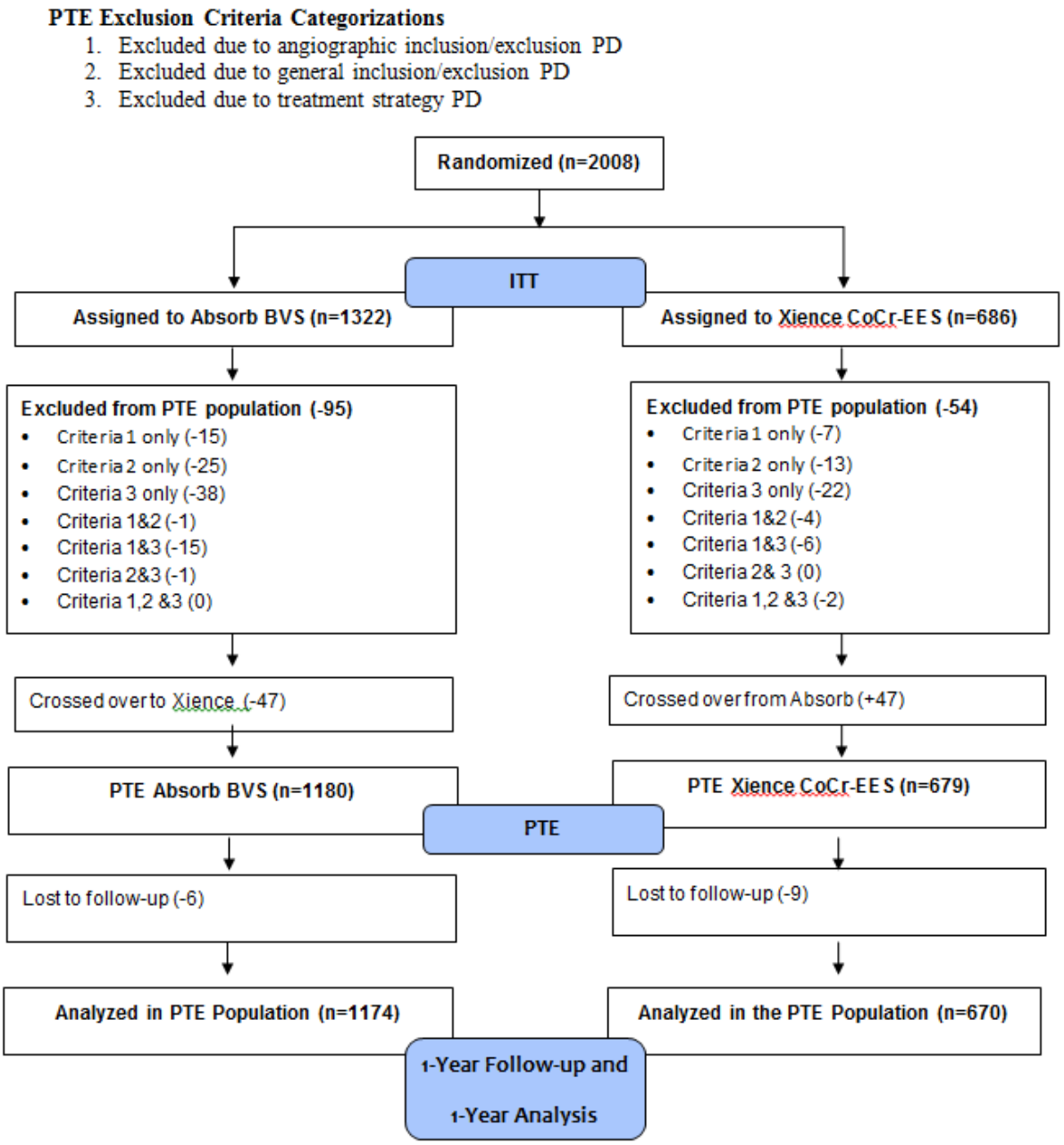


Figure 5.2.1-3 Subject Flow and 1-Year Follow-Up in Per-Treatment-Evaluable Population

In addition to the pre-specified ITT and PTE population analyses, a post-hoc analysis of the AT population was conducted. **Figure 5.2.1-4** presents the subject flow from the ITT population to the AT population. Of the 1322 subjects assigned to the Absorb arm, 1252 subjects (the As-Treated) received Absorb to treat their target lesion(s). The factors contributing to the reduction from the ITT to the AT population in the Absorb arm were 55 cases of crossover to Xience use, mixed use of devices (i.e. Absorb and additional device) on

the target lesion, only non-study device used on the target lesion and no device implanted at the target lesion. In the Xience arm, there was a net increase from the ITT to the AT population (from 686 to 735) mainly because of the crossovers from the Absorb arm. After accounting for terminations, subjects withdrawing consent from the study and the subject with the death, MI and revascularization (DMR) event prior to termination, the number of subjects analyzed at 1 year in the AT population was N = 1245 in the Absorb arm and N = 726 in the Xience arm.

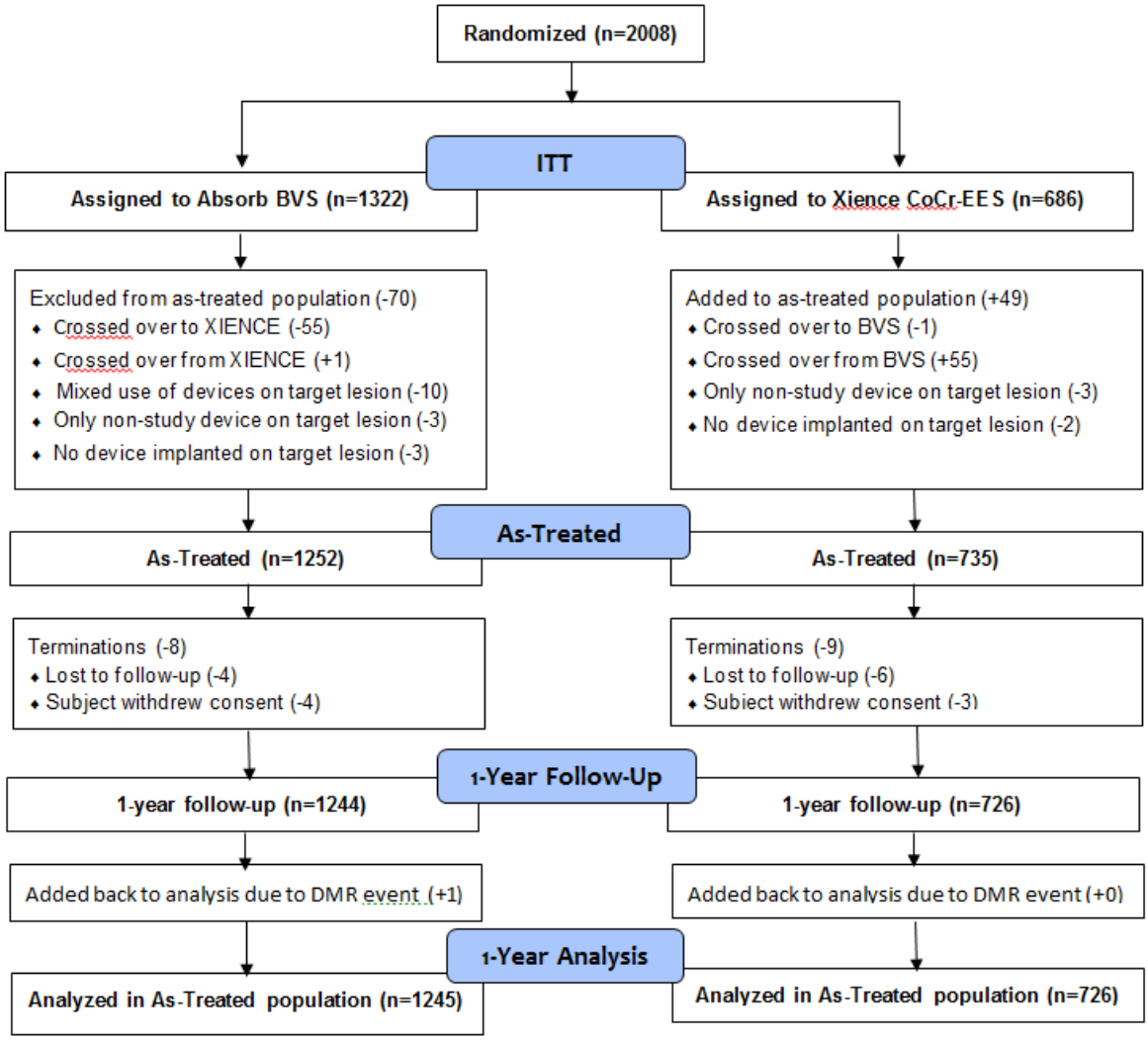


Figure 5.2.1-4 Subject Flow and 1-Year Follow-Up in As-Treated Population

The reasons for subjects not receiving the assigned device have not been reviewed by the FDA and are summarized in **Table 5.2.1-1**. There were a total of 71[3] occurrences in the Absorb arm, for which the most common reasons were failure to deliver / cross / deploy (40 occurrences), lack of Absorb inventory (12 occurrences) and implanted assigned device and other device at target lesion due to bailout (10 occurrences). There were a total of 6 occurrences in the Xience arm.

Table 5.2.1-1 Reasons for Unassigned Devices

	Absorb		Xience	
	N	**%**	**N**	**%**
Failure to Deliver / Cross	40	56%	2	33%
Implanted assigned device and other device at target lesion due to bailout	10	14%	0	0%
Lack of BVS Inventory	12	17%	0	0%
Other Device Issues*	4	5.6%	1	17%
Randomization error/Physician Decision	4	5.6%	2	33%
Unknown	1	1.4%	1	17%
Total	71	100.0%	6	100.0%

* Other device issues in Absorb arm include: 1 incorrect guide liner size used; 1 guide catheter broke; 1 device damage; 1 due to temperature tag excursion

The key baseline demographics and risk factors in the ITT population are shown in **Table 5.2.1-2**. All baseline characteristics were balanced between the study arms, and were representative of those found in DES approval trials. Approximately one third of subjects had diabetes mellitus. There was high prevalence of hypertension and dyslipidemia. Approximately 70% presented with stable coronary artery disease while about 30% had a recent acute coronary syndrome (ACS) or MI where biomarkers had returned to normal.

[3] Note that the 71 subjects in the Absorb arm accounts for the 1 patient that crossed over to the Absorb arm from the Xience arm

Table 5.2.1-2 Key Baseline Subject Characteristics and Risk Factors – Per-Subject Analysis, Intent-to-Treat Population

	Absorb (N=1322)	Xience (N=686)	p-value
Characteristic			
Age (year)	63.5 ± 10.6 (1322)	63.6 ± 10.3 (686)	0.75
Male Subjects	70.7% (934/1322)	70.1% (481/686)	0.80
Current Tobacco Use	21.3% (281/1322)	20.7% (142/686)	0.77
Any Diabetes Mellitus (DM)	31.5% (416/1320)	32.7% (224/686)	0.60
Hypertension	84.9% (1122/1322)	85.0% (583/686)	0.95
Dyslipidemia	86.2% (1140/1322)	86.3% (592/686)	0.97
Prior MI	21.5% (282/1311)	22.0% (150/681)	0.79
Clinical Presentation			
Stable CAD	70.3% (929/1321)	72.9% (500/686)	0.23
Recent ACS or MI	29.7% (392/1321)	27.1% (186/686)	0.23

Procedural Antiplatelet Medication Usage

Index procedure usage of antiplatelet medication is shown in **Table 5.2.1-3**. Procedural antiplatelet medication usage was comparable between the Absorb and Xience arms. Almost all subjects received aspirin and a P2Y12 receptor inhibitor, of which clopidogrel was used in approximately 63% of cases, with the remainder using prasugrel or ticagrelor.

Table 5.2.1-3 Antiplatelet Medication Usage for the Index Procedure – Per-Subject Analysis, Intent-to-Treat Population

	Absorb (N=1322)	Xience (N=686)	p-value
Aspirin	99.3% (1313/1322)	99.3% (681/686)	1.0
P2Y12 Receptor Antagonist	99.0% (1309/1322)	98.8% (678/686)	0.70
Clopidogrel Usage	62.6% (827/1322)	64.7% (444/686)	0.34
Prasugrel or Ticagrelor Usage	36.5% (483/1322)	34.4% (236/686)	0.34

Note: Pre-procedure loading is based on the time periods between 24 hours before the procedure and 1 hour post procedure.
Note: Subjects on chronic Prasugrel or Ticagrelor for ≥ 7 days prior to the index procedure are counted as receiving loading dose of P2Y12 Receptor antagonist.

Vessel and Lesion Characteristics

The key vessel and lesion characteristics are shown in **Table 5.2.1-4**. Vessel and lesion characteristics were generally balanced between the study arms. The target vessel was equally distributed between the left anterior descending, the right coronary artery, and the left circumflex artery. Approximately 30% of the lesions were A/B1 (simple) by ACC/AHA classification, while the remainder were B2/C (moderately complex or complex).

Table 5.2.1-4 Vessel and Lesion Characteristics – Per-Subject Analysis, Intent-to-Treat Population

	Absorb (N=1322) (L=1385)	Xience (N=686) (L=713)	p-value
Target Vessel			
Left anterior descending	44.5% (617/1385)	42.2% (301/713)	0.31
Right coronary artery	29.2% (404/1385)	27.2% (194/713)	0.35
Left circumflex or ramus	26.2% (363/1385)	30.6% (218/713)	0.03
ACC/AHA Lesion Class			
A / B1	31.3% (432/1381)	27.5% (195/708)	0.08
B2 / C	68.7% (949/1381)	72.5% (513/708)	0.08

N = Number of Subjects; L= Number of Lesions

Procedural Characteristics and Acute Outcomes

The key vessel and lesion characteristics and procedural variables are shown in **Table 5.2.1-5**. Vessel and lesion characteristics were generally balanced between the study arms. Core laboratory-assessed lesion lengths by quantitative coronary angiography (QCA) were approximately 13 mm; slightly shorter in Absorb versus Xience, though not a clinically relevant difference. Both study arms had approximately 65% diameter stenosis before the procedure. The total device lengths in both arms were approximately 20 millimeters, yielding a device to lesion length ratio of approximately 1:5:1. Maximum balloon diameter was slightly larger with Absorb than Xience, although the difference of 0.06 mm is not clinically relevant. The maximum inflation pressures used to implant Absorb were lower than used for Xience. Post-dilatation was more frequent with Absorb compared to Xience (64.8% vs. 49.9%).

An additional procedural detail that must be noted is that median number of Absorb implanted per investigator was 2.0 among the 490 investigators that implanted Absorb. The minimum number of Absorb implanted per investigator was 1 and the maximum was 37. The median value 2.0 demonstrates limited experience in usage of Absorb.

Table 5.2.1-5 Procedural Characteristics (1) – Per-Subject Analysis, Intent-to-Treat Population

	Absorb (N=1322) (L=1385)	Xience (N=686) (L=713)	p-value
Pre-Procedure QCA			
Lesion length, mm	12.6 ± 5.4 (1378)	13.1 ± 5.8 (708)	0.05
Reference vessel diameter, mm	2.67 ± 0.45 (1380)	2.65 ± 0.46 708)	0.36
Minimal lumen diameter, mm	0.92 ± 0.37 (1380)	0.90 ± 0.34 (708)	0.11
% DS	65.3 ± 12.5 (1380)	65.9 ± 11.7 (708)	0.24
Device Deployment			
Total device length, mm	20.5 ± 7.2 (1380)	20.7 ± 9.0 (708)	0.56
Max device diameter, mm	3.18 ± 0.43 (1384)	3.12 ± 0.45 (711)	0.007
Max balloon pressures, atm	12.4 ± 2.9 (1382)	13.2 ± 2.8 (711)	<0.0001
Post-Dilatation	64.8% (898/1385)	49.9% (356/713)	<0.0001

Additional procedural characteristics are shown in **Table 5.2.1-6**. The most notable differences between arms was in unassigned devices implanted (6.0% vs. 0.6%, $p < 0.001$) and procedure duration (42.2 ± 23.1 min vs. 38.3 ± 20.9 min, $p < 0.001$).

Table 5.2.1-6 Procedural Characteristics (2) – Per-Subject Analysis, Intent-to-Treat Population

	Absorb (N=1322) (L=1385)	Xience (N=686) (L=713)	p-value
Per Subject			
Bivalirudin use	60.7% (803/1322)	58.7% (403/686)	0.39
GP IIb/IIIa inhibitor use	10.1% (133/1322)	12.4% (85/686)	0.11
Any unassigned devices implanted	6.0% (79/1322)	0.6% (4/686)	<0.001
Unplanned overlapping devices	6.2% (82/1322)	8.5% (58/686)	0.06
Intravascular imaging guidance	11.2% (146/1302)	10.8% (73/673)	0.81
Procedure duration (min)	42.2 ± 23.1(1322)	38.3 ± 20.9 (686)	<0.001

Final core laboratory-assessed QCA results are shown in **Table 5.2.1-7**. There were slight differences between arms depending on whether the results were assessed as being in-device, that is from edge to edge of the device, or in-segment, which includes the device itself plus a

5 millimeter proximal and distal margin on each side. The in-segment angiographic measures of acute gain, minimum lumen diameter and %DS, which have a stronger correlation with subsequent adverse events than in-device measures, had no significant differences between arms.

Table 5.2.1-7 Procedural Characteristics (3) – Per-Subject Analysis, Intent-to-Treat Population

	Absorb (N=1322) (L=1385)	**Xience (N=686) (L=713)**	**p-value**
Final Results by QCA			
Reference vessel diameter, mm	2.70 (1374)	2.68 (706)	0.33
In-device			
Acute gain, mm	1.45 (1372)	1.59 (706)	<0.0001
Minimal lumen diameter, mm	2.37 (1373)	2.49 (706)	<0.0001
% DS	11.6 (1369)	6.4 (702)	<0.0001
In-segment			
Acute gain, mm	1.23(1373)	1.24 (706)	0.50
Minimal lumen diameter, mm	2.15 (1374)	2.14 (706)	0.58
% DS	20.0 (1374)	19.8 (706)	0.55

Acute success results are summarized in **Table 5.2.1-8**. Due to the differences between arms in in-device acute expansion and crossover rate, the lesion-level device success rate was lower with Absorb compared to Xience. However, for subject level procedural success, which accounts for angiographic lesion outcomes and in-hospital complications, there were no significant differences between Absorb and Xience.

Table 5.2.1-8 Acute Outcomes – Intent-to-Treat Population

	Absorb (N=1322) (L=1385)	**Xience (N=686) (L=713)**	**p-value**
Device Success (per lesion)	94.3% (1278/1355)	99.3% (699/704)	<0.0001
Procedure Success (per subject)	94.6% (1240/1311)	96.2% (652/678)	0.12

Device Success (lesion basis)

- Successful delivery and deployment of study scaffold/stent at intended target lesion
- Successful withdrawal of delivery system and final in-scaffold/stent DS <30% (QCA)

Procedure Success (subject basis)

- Successful delivery and deployment of at least one study scaffold/stent at intended target lesion
- Successful withdrawal of delivery system and final in-scaffold/stent DS <30% (QCA)
- No in-hospital (maximum 7 days) TLF

Antiplatelet agent use at 30 days and 1 year is summarized in **Table 5.2.1-9**. Antiplatelet usage was approximately 99% at 30 days, and remained high at approximately 95% at 1 year, as expected. Usage rates of aspirin and P2Y12 receptor inhibitor use were similar between the two arms. From 30 days to 1 year, there was a conversion toward relatively higher usage of prasugrel or ticagrelor compared to clopidogrel with Absorb compared to Xience, a difference of approximately 4% which was borderline statistically significant.

Table 5.2.1-9 Antiplatelet Agent Use at 30 Days and 1 Year – Per-Subject Analysis, Intent-to-Treat Population

	Absorb (N=1322) %	Xience (N=686) %	p-value
Use at 30 days			
Aspirin	98.6 (1303/1322)	99.0 (679/686)	0.43
P2Y12 receptor inhibitor	99.0 (1309/1322)	99.1(680/686)	0.81
Clopidogrel	68.3 (903/1322)	72.0 (494/686)	0.09
Prasugrel or ticagrelor	32.4 (428/1322)	28.1(193/686)	0.05
Use at 1 year			
Aspirin	95.8 (1267/1322)	95.8 (657/686)	0.94
P2Y12 receptor inhibitor	94.4 (1248/1322)	95.0 (652/686)	0.55
Clopidogrel	67.5 (893/1322)	72.2 (495/686)	0.03
Prasugrel or ticagrelor	26.9 (355/1322)	22.9 (157/686)	0.05

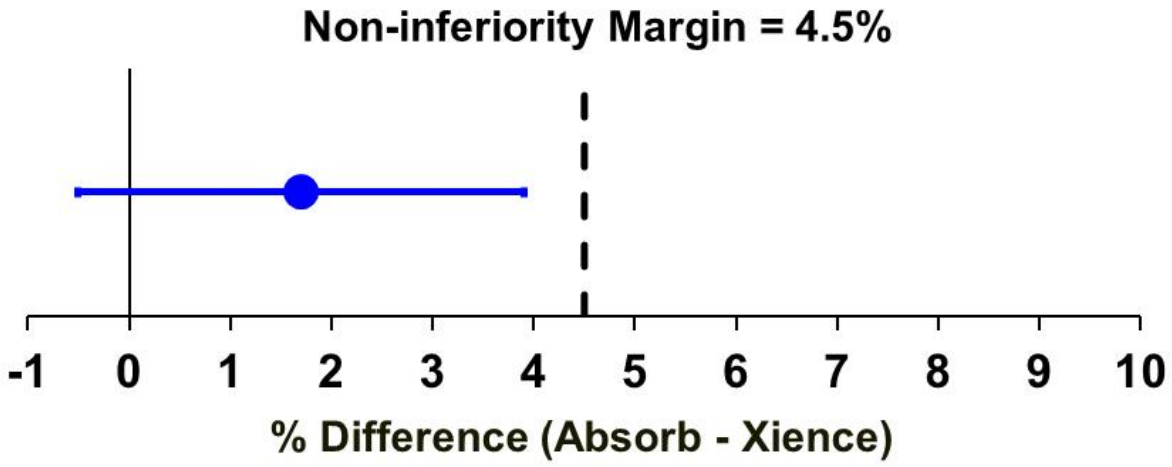
5.2.2 Safety and Effectiveness Results

Primary Endpoint

The ABSORB III trial met its primary endpoint of non-inferiority of Absorb compared to Xience in target lesion failure (TLF) at 1 year as assessed in the ITT population, with rates of 7.8% in the Absorb arm and 6.1% in the Xience arm (non-inferiority p-value = 0.007) (**Table 5.2.2-1**, below). The difference between arms was 1.7%. By 95% confidence interval this could range from 0.5% better with Absorb to 3.9% worse. As depicted in the graph below, the confidence interval of the difference between Absorb versus Xience crosses the line of unity, denoting a non-statistical difference between arms. Additionally, the upper bound of the confidence interval is below the pre-established non-inferiority margin of 4.5%. Thus, the non-inferiority margin was met with high statistically significance, with a p-value of 0.007.

Table 5.2.2-1 Primary Endpoint Analysis – Per-Subject Analysis, Intent-to-Treat Population

Population	Absorb	Xience	Difference (95% CI)	Non-Inferiority P-Value
ITT	7.8% (102/1313)	6.1% (41/677)	1.7% (-0.5%, 3.9%)	0.007



The Kaplan-Meier curve showing the cumulative incidence rates of TLF through 1 year in the ITT population is found in **Figure 5.2.2-1**. Data is shown through 13 months, the outside limit of the one-year follow-up window. Note that due to the difference in statistical algorithms, the Kaplan-Meier estimates of event rates differ slightly from the binary event rates reported in **Table 5.2.2-1**.

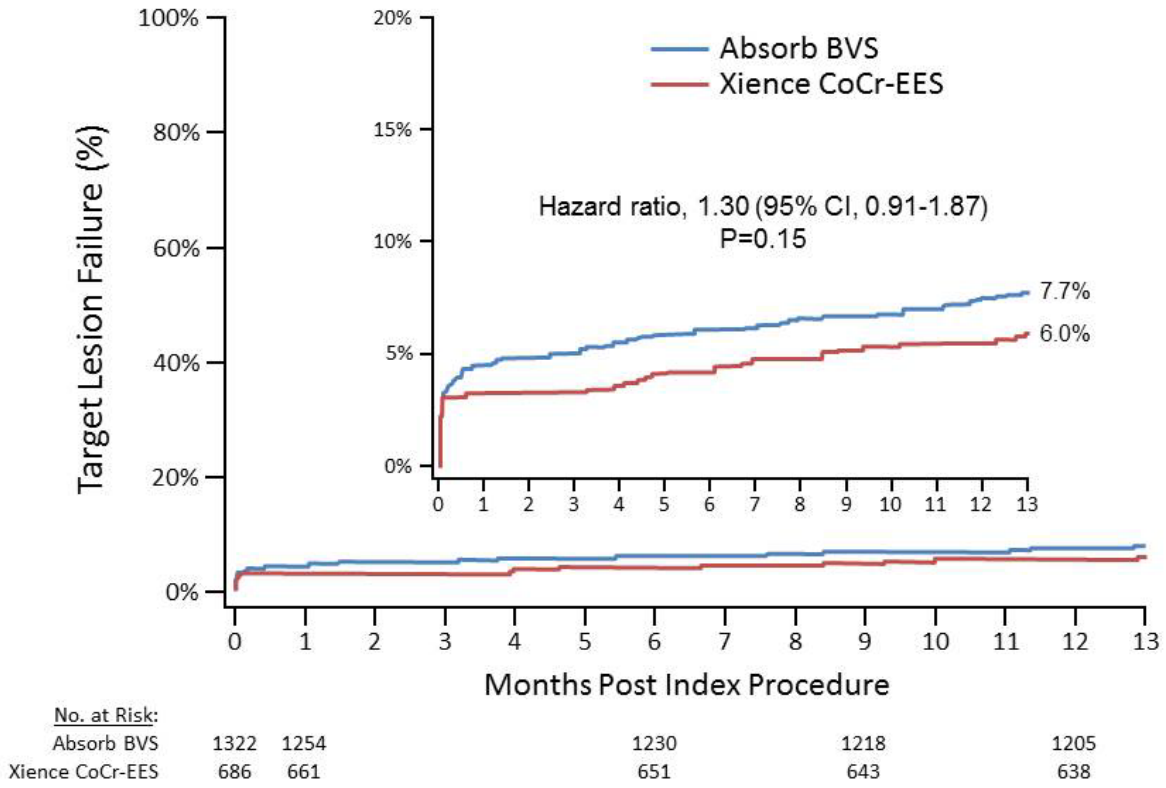


Figure 5.2.2-1 Kaplan-Meier Curves Representing the Estimated Cumulative Incidence Rates of TLF through 1 Year in the Intent-to-Treat Population

The study results as evaluated in the PTE population, depicted in **Table 5.2.2-2**, were positive and consistent with those in the ITT population. The primary endpoint of non-inferiority of Absorb compared to Xience in target lesion failure (TLF) at 1 year was met with rates of 7.8% in the Absorb arm and 5.7% in the Xience arm (non-inferiority p-value = 0.018). As depicted in the table, the confidence interval of the difference between arms also crosses the line of unity, denoting a non-statistical difference, and the upper bound of the confidence interval is below the pre-established non-inferiority margin of 4.5%.

Table 5.2.2-2 Primary Endpoint Analysis – Per-Subject Analysis, Per-Treatment-Evaluable Population

Population	Absorb	Xience	Difference (95% CI)	Non-Inferiority P-Value
PTE	7.8% (91/1174)	5.7% (38/670)	2.08% (-0.19%, 4.35%)	0.0183

Except for the primary endpoint assessment, in the AT population, all results presented for the AT population in **Section 5.2.2** have not been reviewed by the FDA. The study results as evaluated in the AT population, depicted in **Table 5.2.2-3**, were positive and consistent with those in the ITT population. The primary endpoint of non-inferiority of Absorb compared to Xience in target lesion failure (TLF) at 1 year was met with rates of 8.0% in the Absorb arm and 6.1% in the Xience arm (non-inferiority p-value = 0.011). The difference between arms was 1.9%. As depicted in the graph below, the confidence interval of the difference between arms also crosses the line of unity, denoting a non-statistical difference, and the upper bound of the confidence interval is below the pre-established non-inferiority margin of 4.5%.

Table 5.2.2-3 Primary Endpoint Analysis – Per-Subject Analysis, As-Treated Population

Population	Absorb	Xience	Difference (95% CI)	Non-Inferiority P-Value
As-Treated	8.0% (99/1245)	6.1% (44/726)	1.9% (-0.35%, 4.1%)	0.011

Subgroup Analysis of Primary Endpoint

Subgroup analyses of the primary endpoint, as summarized in **Figure 5.2.2-2,** showed similar clinical outcomes with no statistical differences in 1-year TLF between the Absorb and Xience arms for all subgroups. Interaction p-values were > 0.05 for all subgroups depicted here, indicating similar relative risks between Absorb versus Xience treatment regardless of age, gender, diabetic status, etc. The only subgroup for which the interaction p-value approached significance was ACC/AHA lesion class, where the relative risk (the degree to which the results favored Xience) was higher for simple A/B1 lesions than in the more complex B2/C lesions. Mechanistically there is no reason why this would be the case.

Subgroup	Absorb N=1322	Xience N=686	Relative Risk (95% CI)	p-value (interaction)
Age ≥64	8.1	5.9	1.37 (0.84-2.23)	0.69
Age <64	7.4	6.2	1.19 (0.72-1.97)	
Female	8.5	7.4	1.16 (0.64-2.08)	0.68
Male	7.4	5.5	1.36 (0.88-2.10)	
Diabetes	10.7	9.1	1.18 (0.71-1.95)	0.68
No Diabetes	6.3	4.6	1.38 (0.85-2.24)	
Unstable Angina/Recent MI	6.5	6.6	0.98 (0.50-1.90)	0.35
Stable CAD	8.3	5.8	1.42 (0.94-2.15)	
Single Lesion Treated	7.7	5.8	1.32 (0.92-1.89)	0.50
Dual Lesion Treated	9.4	11.5	0.81 (0.22-3.01)	
Clopidogrel	8.0	6.8	1.17 (0.77-1.78)	0.43
Prasugrel or Ticagrelor	7.1	4.3	1.63 (0.82-3.25)	
ACC/AHA Class A or B1	6.8	2.2	3.05 (1.08-8.60)	0.07
ACC/AHA Class B2 or C	8.2	7.5	1.10 (0.75-1.61)	
Lesion Length < 11.75 mm	7.9	4.8	1.64 (0.95-2.83)	0.23
Lesion Length ≥ 11.75 mm	7.7	7.3	1.06 (0.67-1.67)	
Vessel Diameter < 2.63 mm	9.8	7.8	1.27 (0.82-1.94)	0.90
Vessel Diameter ≥ 2.63 mm	5.7	4.3	1.34 (0.73-2.44)	

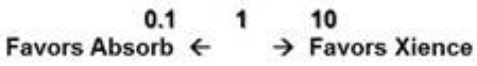


Figure 5.2.2-2 ABSORB III Subgroup Analysis Summary Comparing Absorb and Xience Arms for 1-Year TLF

Results of the components of the primary endpoint are shown for the ITT population in **Table 5.2.2-4** and the AT population in **Table 5.2.2-5**. For the primary endpoint TLF and for cardiac death, target vessel related myocardial infarction (TV-MI), and ischemia-driven target lesion revascularization (ID-TLR), the rates were low and not statistically significant for Absorb compared to Xience in both populations.

Table 5.2.2-4 Components of Primary Endpoint – Per-Subject Analysis, Intent-to-Treat Population

	Overall ITT population		
	Absorb (N=1322)	**Xience (N=686)**	**P-value***
TLF	7.8% (102/1313)	6.1% (41/677)	0.16
Cardiac Death	0.6% (8/1313)	0.1% (1/677)	0.29
TV- MI	6.0% (79/1313)	4.6% (31/677)	0.18
ID-TLR	3.0% (40/1313)	2.5% (17/677)	0.50

TV-MI = target vessel myocardial infarction
ID-TLR = ischemia-driven target lesion revascularization
*Not pre-specified and not adjusted for multiplicity

Table 5.2.2-5 Components of Primary Endpoint – Per-Subject Analysis, As-Treated Population

	Overall As Treated population		
	Absorb (N=1252)	**Xience (N=735)**	**P-value***
TLF	8.0% (99/1245)	6.1% (44/726)	0.12
Cardiac Death	0.6% (8/1245)	0.1% (1/726)	0.17
TV- MI	6.1% (76/1245)	4.7% (34/726)	0.18
ID-TLR	3.1% (39/1245)	2.5% (18/726)	0.40

TV-MI = target vessel myocardial infarction
ID-TLR = ischemia-driven target lesion revascularization
*Not pre-specified and not adjusted for multiplicity

Secondary Endpoint Analysis

Safety

Results of all-cause death, all MI and TV-MI are shown for the ITT population in **Table 5.2.2-6** and for the AT population in **Table 5.2.2-7**. For all endpoints, evaluated at 30 days or at 1 year, outcome rates were low for both arms. Absorb had slightly higher rates compared to Xience but the difference was not statistically significantly different between Absorb versus Xience. These observations were consistent between the ITT and AT populations.

All secondary endpoint results for 1-year safety and effectiveness are presented in **Table 5.2.2-13** and **Table 5.2.2-14**.

Table 5.2.2-6 All-Cause Death and MI – Per-Subject Analysis, Intent-to-Treat Population

	Absorb (N=1322)	Xience (N=686)	P-Value*
Cardiac Death/All MI			
30 days	4.6% (61/1317)	3.5% (24/686)	0.23
1 year	7.5% (98/1313)	5.8% (39/677)	0.16
All Cause Death			
30 days	0.4% (5/1317)	0.0% (0/686)	0.17
1 year	1.1% (15/1313)	0.4% (3/677)	0.12
All MI			
30 days	4.3% (57/1317)	3.5% (24/686)	0.37
1 year	6.9% (90/1313)	5.6% (38/677)	0.28
TV-MI			
30 days	4.3% (56/1317)	3.2% (22/686)	0.25
1 year	6.0% (79/1313)	4.6% (31/677)	0.18

*Not pre-specified and not adjusted for multiplicity

Table 5.2.2-7 All-Cause Death and MI – Per-Subject Analysis, As-Treated Population

	Absorb (N=1252)	Xience (N=735)	P-Value*
Cardiac Death/All MI			
30 days	4.6% (58/1249)	3.7% (27/735)	0.30
1 year	7.6% (94/1245)	5.9% (43/726)	0.17
All Cause Death			
30 days	0.4% (5/1249)	0.0% (0/735)	0.16
1 year	1.1% (14/1245)	0.6% (4/726)	0.20
All MI			
30 days	4.3% (54/1249)	3.7% (27/735)	0.48
1 year	6.9% (86/1245)	5.8% (42/726)	0.33
TV-MI			
30 days	4.2% (53/1249)	3.4% (25/735)	0.35
1 year	6.1% (76/1245)	4.7% (34/726)	0.18

Note: the sample sizes N represent the 1-year analysis populations
*Not pre-specified and not adjusted for multiplicity

Details of peri-procedural MI based on different biomarker enzyme elevations – the per-protocol definition of TV-MI is based on an elevation level of > 5x ULN – are shown in **Table 5.2.2-8** for the ITT population and in **Table 5.2.2-9** for the AT population. Absorb is similar to Xience in peri-procedure MI regardless of elevation level, and the occurrence of clinically significant elevations (> 10x ULN) is very low for both arms. There was concern of potentially higher rates in peri-procedural MI in the Absorb arm because its thicker struts could potentially cover small side branches resulting in cardiac enzyme elevations. However, this proved not to be the case. Regardless of the definition used for peri-

procedural MI – the protocol definition of a CK-MB > 5x ULN, the more sensitive CK-MB > 3x ULN or the clinically relevant definition from Society of Cardiac Angiography and Interventions (SCAI)- the observed rates were similar between Absorb and Xience, as evaluated in both the ITT and AT populations.

Table 5.2.2-8 Peri-procedural MI Based on Different Cardiac Biomarker Elevations – Per-Subject Analysis, Intent-to-Treat Population

	Absorb (N=1322)	Xience (N=686)	Relative Risk [95% CI]	P-Value*
CK-MB >3x ULN	6.8% (89/1315)	6.6% (45/682)	1.03 [0.73, 1.45]	0.89
CK-MB >5x ULN	3.0% (40/1315)	2.8% (19/682)	1.09 [0.64, 1.87]	0.75
CK-MB >8x ULN	1.3% (17/1315)	1.3% (9/682)	0.98 [0.44, 2.19]	0.96
CK-MB >10x ULN	0.9% (12/1315)	1.2% (8/682)	0.78 [0.32, 1.89]	0.58
SCAI definition*	0.9% (12/1315)	1.2% (8/682)	0.78 [0.32, 1.89]	0.58

*Clinically relevant MI: CK-MB >10x ULN or >5x ULN with new Q waves [65]
*Not pre-specified and not adjusted for multiplicity

Table 5.2.2-9 Peri-procedural MI Based on Different Cardiac Biomarker Elevations – Per-Subject Analysis, As-Treated Population

	Absorb (N=1252)	Xience (N=735)	Relative Risk [95% CI]	P-Value*
CK-MB >3x ULN	6.3% (78/1245)	7.4% (54/731)	0.85 [0.61, 1.19]	0.33
CK-MB >5x ULN	3.1% (38/1245)	2.9% (21/731)	1.06 [0.63, 1.80]	0.82
CK-MB >8x ULN	1.3% (16/1245)	1.4% (10/731)	0.94 [0.43, 2.06]	0.88
CK-MB >10x ULN	0.9% (11/1245)	1.2% (9/731)	0.72 [0.30, 1.72]	0.46
SCAI definition*	0.9% (11/1245)	1.2% (9/731)	0.72 [0.30, 1.72]	0.46

*Clinically relevant MI: CK-MB >10x ULN or >5x ULN with new Q waves [65].
*Not pre-specified and not adjusted for multiplicity

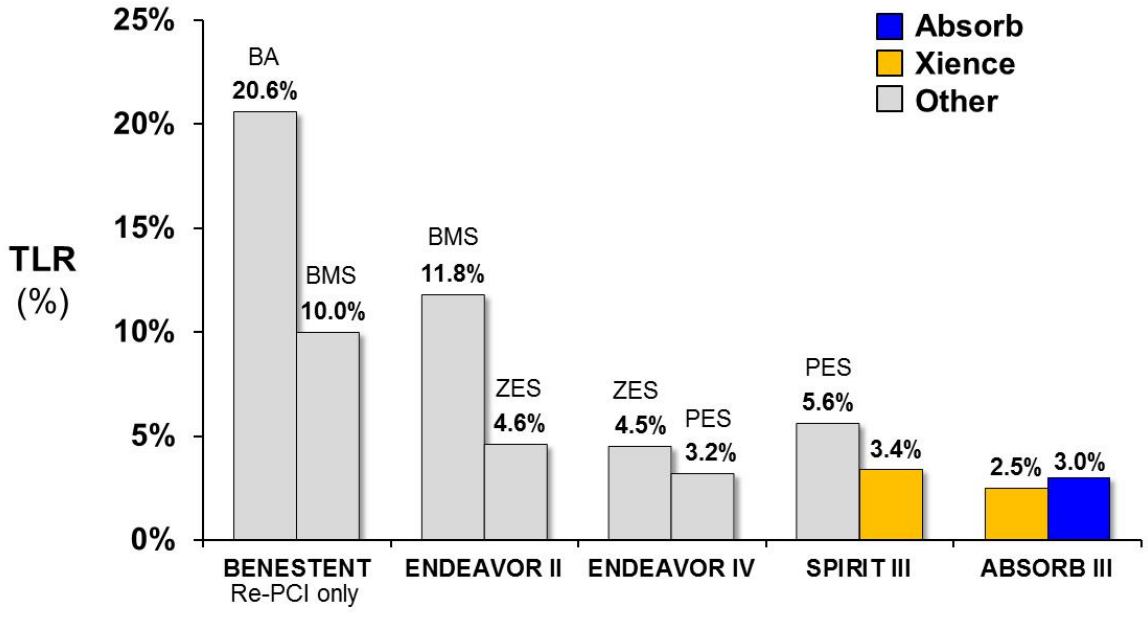
Stent / scaffold thrombosis observed on a cumulative basis through 1 year is summarized in **Table 5.2.2-13** and **Table 5.2.2-14** for the ITT and AT populations, respectively. The definite/probable rates for Absorb and Xience were 1.54% vs. 0.74% (p = 0.13) in the ITT population and 1.54% vs. 0.83% (p = 0.18) in the AT population. Absorb had a higher observed rate compared to Xience but this difference of 0.8% was not statistically different. If the 1-year follow-up period is divided into periods of < 30 days and 30 days to 1 year,

there also no statistically significant differences. Similarly, if the 1-year definite/probable assessment is divided into definite or probable assessments, there are no statistically significant differences in thrombosis rates for either the ITT or AT populations.

Effectiveness

The effectiveness assessment of ischemia-driven TLR were very similar between the two device arms in which there was only a 0.5% difference (**Table 5.2.2-4)**. As explained prior, angina, ID-TVR and all revascularization were tested for superiority based on signals of a possible advantage of Absorb compared to Xience in prior trials. As seen for the ITT, PTE, and ATT populations in **Tables 5.2.2-10**, **5.2.2-11**, and **5.2.2-12**, respectively, statistical significance was not observed between Absorb and Xience for these endpoints. However, the 1-year observations of angina and revascularization represent very good outcomes for both devices. These observations demonstrate that Absorb and Xience are comparable in effectiveness as it pertains to angina and the revascularization endpoints.

To demonstrate that Absorb preserves the effectiveness of current-day metallic DES compared to prior treatments of PTCA and BMS, **Figure 5.2.2-3** shows the evolution of TLR rates over the era of stenting, beginning with the BENESTENT trial which evaluated BMS versus BA [6, 7, 10, 11]. The low revascularization rates of Absorb in ABSORB III represent a continuation in the effectiveness profile offered by DES.



Note: ENDEAVOR II outcomes data represents at 270 days.

Figure 5.2.2-3 Evolution of PCI TLR Outcomes

Table 5.2.2-10 Powered Secondary Endpoint Analysis - Per-Subject Analysis (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: For the angina endpoint, denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through 1 year without
any angina event. For the all revascularization endpoint, denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through 1 year without any DMR event (all death, all MI (regardless of MI definition), all revascularization, respectively).
Note: 1-year timeframe includes a window of +/- 28 days.
Note: N is the total number of subjects.

Table 5.2.2-11 Powered Secondary Endpoint Analysis - Per-Subject Analysis (Primary Analysis Group, Per-Treatment-Evaluable Population)

	Absorb (N=1180)	XIENCE (N=679)	Difference [95% CL][4]	Superiority P-Value[5]
Powered Secondary Endpoint				
1-Year Angina[1]	17.4% (203/1164)	19.0% (127/670)	-1.52% [-5.20%, 2.17%]	0.4159
1-Year All Revascularization[2]	8.2% (96/1174)	8.4% (56/670)	-0.18% [-2.80%, 2.44%]	0.9299
1-Year ID-TVR[3]	4.9% (57/1174)	3.7% (25/670)	1.12% [-0.77%, 3.01%]	0.2914

[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: For the angina endpoint, denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through 1 year without
any angina event. For the all revascularization endpoint, denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through 1 year without any DMR event (all death, all MI (regardless of MI definition), all revascularization, respectively).
Note: 1-year timeframe includes a window of +/- 28 days.
Note: N is the total number of subjects.

Table 5.2.2-12 Powered Secondary Endpoint Analysis – Per-Subject Analysis (Primary Analysis Group, As-Treated Population)

	Absorb (N=1252)	XIENCE (N=735)	Difference [95% CL][4]	Superiority P-Value[5]
Powered Secondary Endpoint				
1-Year Angina[1]	18.3% (226/1236)	18.6% (135/726)	-0.31% [-3.87%, 3.25%]	0.8640
1-Year All Revascularization[2]	8.9% (111/1245)	8.8% (64/726)	0.10% [-2.50%, 2.70%]	1.0000
1-Year ID-TVR[3]	5.1% (63/1245)	3.9% (28/726)	1.20% [-0.65%, 3.06%]	0.2657

[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: For the angina endpoint, denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through 1 year without
any angina event. For the all revascularization endpoint, denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through 1 year without any DMR event (all death, all MI (regardless of MI definition), all revascularization, respectively).
Note: 1-year timeframe includes a window of +/- 28 days.
Note: N is the total number of subjects.

Table 5.2.2-13 Safety and Effectiveness Endpoints in ITT Population

	Absorb (N=1322)	Xience (N=686)	Relative Risk [95% CI]	P-value*
Target lesion failure	7.8% (102/1313)	6.1% (41/677)	1.28 [0.90, 1.82]	0.16
Cardiac death	0.6% (8/1313)	0.1% (1/677)	4.12 [0.52, 32.91]	0.29
Target-vessel MI	6.0% (79/1313)	4.6% (31/677)	1.31 [0.88, 1.97]	0.18
ID-TLR	3.0% (40/1313)	2.5% (17/677)	1.21 [0.69, 2.12]	0.50
All-cause mortality	1.1% (15/1313)	0.4% (3/677)	2.58 [0.75, 8.87]	0.12
All myocardial infarction	6.9% (90/1313)	5.6% (38/677)	1.22 [0.85, 1.76]	0.28
Q-wave	0.8% (10/1313)	0.4% (3/677)	1.72 [0.47, 6.22]	0.56
Non-Q-wave	6.1% (80/1313)	5.2% (35/677)	1.18 [0.80, 1.73]	0.40
Periprocedural	3.1% (41/1313)	3.2% (22/677)	0.96 ([0.58, 1.60]	0.88
Non-peri-procedural	3.7% (49/1313)	2.4% (16/677)	1.58 [0.90, 2.76]	0.10
All revascularization	9.1% (120/1313)	8.1% (55/677)	1.12 [0.83, 1.53]	0.45
Ischemia-driven	8.8% (115/1313)	8.0% (54/677)	1.10 [0.81, 1.50]	0.55
TVR	5.0% (66/1313)	3.7% (25/677)	1.36 [0.87, 2.14]	0.18
Non-TVR	5.4% (71/1313)	5.8% (39/677)	0.94 [0.64, 1.37]	0.74
Non-ischemia driven	0.6% (8/1313)	0.7% (5/677)	0.82 [0.27, 2.51]	0.77
TLR	0.2% (2/1313)	0.3% (2/677)	0.52 [0.07, 3.65]	0.61
TVR	0.2% (3/1313)	0.4% (3/677)	0.52 [0.10, 2.55]	0.42
Non-TVR	0.4% (5/1313)	0.3% (2/677)	1.29 [0.25, 6.63]	1.00
Angina (subject-reported)	18.3% (238/1302)	18.4% (125/678)	0.99 [0.82, 1.21]	0.93
Device thrombosis (definite/probable)	1.54% (20/1301)	0.74% (5/675)	2.08 [0.78, 5.51]	0.13
Early (0 - 30 days)	1.06% (14/1315)	0.73% (5/686)	1.46 [0.53, 4.04]	0.46
Acute (≤24 hours)	0.15% (2/1320)	0.58% (4/686)	0.26 [0.05, 1.42]	0.19
Subacute (>24 hours - 30 days)	0.91% (12/1315)	0.15% (1/686)	6.26 [0.82, 48.04]	0.04
Late (31 days - 1 year)	0.46% (6/1299)	0.00% (0/675)	-	0.10
Definite (through 1 year)	1.38% (18/1301)	0.74% (5/675)	1.87 [0.70, 5.01]	0.21
Probable (through 1 year)	0.15% (2/1301)	0.00% (0/675)	-	0.55

*Not pre-specified and not adjusted for multiplicity

Table 5.2.2-14 Safety and Effectiveness Endpoints in As Treated Population

	Absorb (N=1252)	Xience (N=735)	Relative Risk [95% CI]	P-value*
Target lesion failure	8.0% (99/1245)	6.1% (44/726)	1.31 [0.93, 1.85]	0.12
Cardiac death	0.6% (8/1245)	0.1% (1/726)	4.67 [0.58, 37.22]	0.17
Target-vessel MI	6.1% (76/1245)	4.7% (34/726)	1.30 [0.88, 1.93]	0.18
Ischemia-driven TLR	3.1% (39/1245)	2.5% (18/726)	1.26 [0.73, 2.19]	0.40
All-cause mortality	1.1% (14/1245)	0.6% (4/726)	2.04 [0.67, 6.18]	0.20
All myocardial infarction	6.9% (86/1245)	5.8% (42/726)	1.19 [0.84, 1.71]	0.33
Q-wave	0.8% (10/1245)	0.4% (3/726)	1.94 [0.54, 7.04]	0.39
Non-Q-wave	6.1% (76/1245)	5.4% (39/726)	1.14 [0.78, 1.65]	0.50
Periprocedural	3.1% (39/1245)	3.3% (24/726)	0.95 [0.57, 1.56]	0.83
Non-peri-procedural	3.8% (47/1245)	2.5% (18/726)	1.52 [0.89, 2.60]	0.12
All revascularization	8.9% (111/1245)	8.8% (64/726)	1.01 [0.75, 1.36]	0.94
Ischemia-driven	8.5% (106/1245)	8.7% (63/726)	0.98 [0.73, 1.32]	0.90
TVR	5.1% (63/1245)	3.9% (28/726)	1.31 [0.85, 2.03]	0.22
Non-TVR	5.1% (64/1245)	6.3% (46/726)	0.81 [0.56, 1.17]	0.26
Non-ischemia driven	0.6% (8/1245)	0.7% (5/726)	0.93 [0.31, 2.84]	1.00
TLR	0.2% (2/1245)	0.3% (2/726)	0.58 [0.08, 4.13]	0.63
TVR	0.2% (3/1245)	0.4% (3/726)	0.58 [0.12, 2.88]	0.68
Non-TVR	0.4% (5/1245)	0.3% (2/726)	1.46 [0.28, 7.49]	1.00
Angina (subject-reported)	18.3% (226/1235)	18.6% (135/726)	0.98 [0.81, 1.19]	0.87
Device thrombosis (definite/probable)	1.54% (19/1234)	0.83% (6/723)	1.86 [0.74, 4.62]	0.18
Early (0 - 30 days)	1.04% (13/1247)	0.82% (6/735)	1.28 [0.49, 3.35]	0.62
Acute (≤24 hours)	0.16% (2/1251)	0.54% (4/735)	0.29 [0.05, 1.60]	0.20
Subacute (>24 hours - 30 days)	0.88% (11/1247)	0.27% (2/735)	3.24 [0.72, 14.59]	0.15
Late (31 days - 1 year)	0.49% (6/1232)	0.00% (0/723)	-	0.09
Definite (through 1 year)	1.38% (17/1234)	0.83% (6/723)	1.66 [0.66, 4.19]	0.28
Probable (through 1 year)	0.16% (2/1234)	0.00% (0/723)	-	0.53

*Not pre-specified and not adjusted for multiplicity

Additional Analyses

Outcomes of Subjects Not Receiving Assigned Device

As described in the subject flow diagram in **Figure 5.2.1-3**, there were 1251 subjects that received an Absorb and 71 subjects that received an unassigned device. **Table 5.2.2-15** summarizes the observed outcomes in the group that received an Absorb (N = 1251) compared to the subjects that did not receive an assigned device (N = 71). There were no statistically significant differences in event rates between the two groups. These results have not been reviewed by FDA.

Table 5.2.2-15 Outcomes of Subjects Not Receiving Assigned Device – Per-Subject Analysis, As-Treated Population

	Received Assigned Device (N=1251)	Not Received Assigned Device (N=71)	P-Value*
TLF	8.0% (99/1244)	4.3% (3/69)	0.28
Cardiac Death	0.6% (8/1244)	0.0% (0/69)	1.0
TV-MI	6.1% (76/1244)	4.3% (3/69)	0.79
ID-TLR	3.1 (39/1244)	1.4% (1/69)	0.72
Define/Probable ST	1.54% (19/1233)	1.47% (1/68)	1.00
0-30 days (early)	1.04% (13/1246)	1.45% (1/69)	0.53
> 30 days-1 year (late)	0.49% (6/1231)	0.00% (0/68)	1.00

Note: 1251 subjects in the as treated population accounts for the removal of 1 subject that crossed over from Xience to Absorb.
* Not pre-specified and not adjusted for multiplicity

Reference Vessel Diameter Analysis

A post-hoc subgroup analysis was performed to assess the impact of vessel size on clinical performance. The current generation of Absorb has thicker struts than Xience (157 microns vs. 81 microns), and thus it is biologically plausible that in very small vessels, the space occupying effect of larger struts might negatively impact outcomes. The subgroup analysis compares event rates between very small vessels to vessels that are appropriately sized for the intended study population. To be included in ABSORB III, subjects were required to have target vessels with a visually estimated RVD of ≥ 2.5 mm and ≤ 3.75 mm. Prior studies have shown that core laboratory-assessed QCA underestimates true vessel dimensions by approximately 0.25 mm compared to visual estimation. Thus, the lower eligibility limit of 2.5 mm by visual estimation would correspond to 2.25 mm by core lab QCA, which was performed on all subjects. Very small vessels where core lab RVD was < 2.25 mm are below the level intended for treatment in ABSORB III; notwithstanding this, baseline analysis

showed that 18.8% of the study population had a lesion treated with RVD < 2.25 mm, by core lab QCA.

The subgroup analysis comparing subjects who had at least one lesion treated with an RVD < 2.25 mm to subjects with all RVD ≥ 2.25 mm found that the baseline and lesion characteristics are mostly similar between subgroups, as summarized in **Appendix 1**. **Figure 5.2.2-4** shows the 1-year TLF rates for subjects with any RVD < 2.25 mm compared with those where all lesions treated had all RVD ≥ 2.25 mm. The Absorb results are depicted in blue and Xience in yellow. There are two observations that can be made from these graphs; 1) the event rates for both devices are higher in very small vessels than in larger vessels; and 2) there is a larger difference in rates between Absorb and Xience in these very small vessels that visually met inclusion criteria for the trial but by QCA were very small vessels < 2.25mm. In contrast, in subjects in which all had an RVD ≥ 2.25 mm, which comprised 81.2% of the study population (over 1600 subjects and by itself larger than any other DES pivotal trial), the TLF rates for both arms are lower and even more comparable than for the overall trial population. There were no significant differences between the two devices for either the < 2.25mm or ≥ 2.25 mm group.

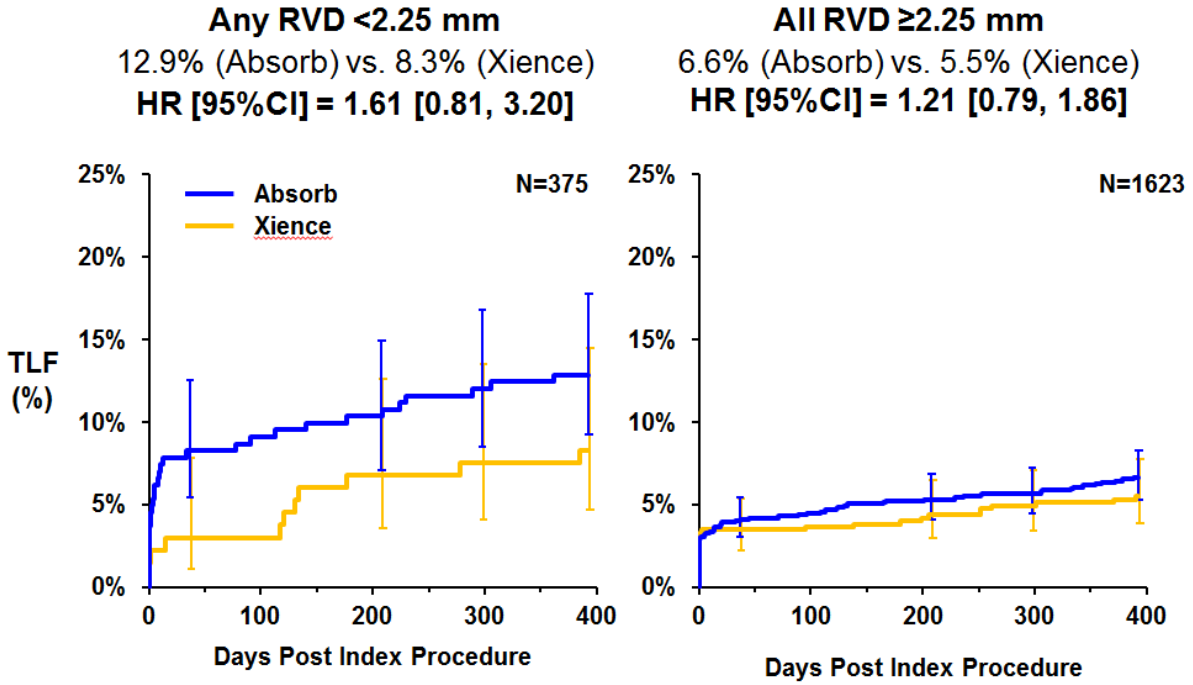


Figure 5.2.2-4 1-Year TLF by Vessel Size: Any RVD < 2.25 mm vs. All RVD ≥ 2.25 mm

The subgroup analysis results show very similar trends for 1-year device thrombosis outcomes, shown in **Figure 5.2.2-5**. In subjects with very small vessels treated, Absorb again showed a larger relative difference in the event rate compared to Xience, although both had higher rates in these vessels. On the other hand, in vessels that are of appropriate size to

be treated with both devices (≥ 2.25mm by QCA) and representing the intended population, the device thrombosis rates are low and similar for Absorb and Xience (0.9% vs. 0.6%, see **Table 5.2.2-16**). There were no significant differences between the two devices for either the < 2.25mm or ≥ 2.25 mm group.

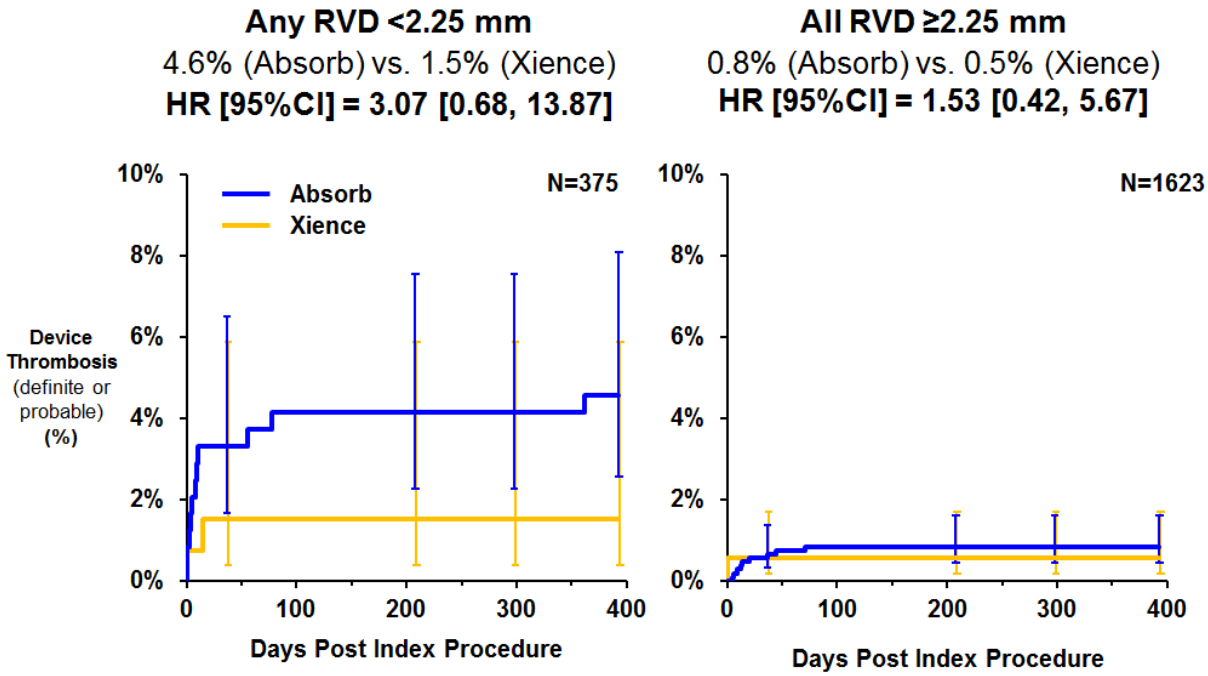


Figure 5.2.2-5 1-Year Device Thrombosis by Vessel Size: Any RVD < 2.25 mm vs. All RVD ≥ 2.25 mm

Table 5.2.2-16 shows the event rates for key outcome measures for the RVD < 2.25 mm subgroup, the RVD ≥ 2.25 mm subgroup and the overall ITT study population. In subjects with RVD ≥ 2.25 mm, most outcome measures had lower rates in both arms than in subjects with very small vessels and the overall population. Importantly, the observed difference in event rates between Absorb and Xience was smaller for most outcome measures in the RVD ≥ 2.25 mm subgroup than in the overall population: 1.2% vs. 1.7% for TLF, 0.4% vs. 0.5% for cardiac death, 0.6% vs. 1.4% for TV-MI, 0.7% vs. 0.5% for ID-TLR and 0.3% vs. 0.8% for device thrombosis, respectively. These findings provide confidence that when Absorb is placed in the appropriate sized vessels, the differences between the two arms are minimal and further improve upon the results in the overall population. Additionally, these findings have important implications on the labeling of the device and physician education, which will be discussed further in **Section 8.0**.

Table 5.2.2-16 Subgroup Information and 1-Year Clinical Outcomes Stratified by Core Laboratory Assessed RVD – Per-Subject Analysis (Primary Analysis Group, Intent-to-Treat Population, Per Protocol MI Definition)

	RVD < 2.25 mm*			RVD ≥ 2.25 mm			Overall ITT Population		
	Absorb (N=242)	**Xience (N=133)**	**P-value****	**Absorb (N=1074)**	**Xience (N=549)**	**P-value****	**Absorb (N=1322)**	**Xience (N=686)**	**P-value****
TLF	12.9% (31/241)	8.3% (11/133)	0.18	6.7% (71/1067)	5.5% (30/542)	0.38	7.8% (102/1313)	6.1% (41/677)	0.16
Cardiac Death	0.8% (2/241)	0.0% (0/133)	0.54	0.6% (6/1067)	0.2% (1/542)	0.43	0.6% (8/1313)	0.1% (1/677)	0.29
TV- MI	10.0% (24/241)	4.5% (6/133)	0.06	5.2% (55/1067)	4.6% (25/542)	0.64	6.0% (79/1313)	4.6% (31/677)	0.18
ID-TLR	6.6% (16/241)	6.8% (9/133)	0.96	2.2% (24/1067)	1.5% (8/542)	0.29	3.0% (40/1313)	2.5% (17/677)	0.50
Device Thrombosis (Def/Prob)	4.6% (11/238)	1.5% (2/133)	0.15	0.9% (9/1058)	0.6% (3/540)	0.76	1.5% (20/1301)	0.7% (5/675)	0.13

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

** Not pre-specified and not adjusted for multiplicity

Diabetes Mellitus Subgroup Analysis

A pre-specified subgroup analysis was performed for diabetes mellitus. **Table 5.2.2-17** shows the key 1-year outcome measures for the overall ITT population, all diabetes mellitus (all DM) subgroup and all non-DM subgroup. Historically, diabetes mellitus is associated with elevated event rates in coronary stent trials, and the ABSORB III results are consistent with this pattern. For the all DM subgroup, the observed clinical event rates in both Absorb and Xience arms were higher than in the overall population for most key outcome measures. Within both subgroups and the overall population, there were no statistical differences for any endpoint comparisons between study arms.

Table 5.2.2-17 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			Overall ITT population		
	Absorb (N=416)	**Xience (N=224)**	**P-value***	**Absorb (N=904)**	**Xience (N=462)**	**P-value***	**Absorb (N=1322)**	**Xience (N=686)**	**P-value***
TLF	10.7% (44/411)	9.1% (20/220)	0.52	6.3% (57/900)	4.6% (21/457)	0.19	7.8% (102/1313)	6.1% (41/677)	0.16
Cardiac Death	0.5% (2/411)	0.0% (0/220)	0.55	0.7% (6/900)	0.2% (1/457)	0.43	0.6% (8/1313)	0.1% (1/677)	0.29
TV- MI	9.0% (37/411)	7.3% (16/220)	0.46	4.6% (41/900)	3.3% (15/457)	0.27	6.0% (79/1313)	4.6% (31/677)	0.18
ID-TLR	5.6% (23/411)	3.6% (8/220)	0.28	1.8% (16/900)	2.0% (9/457)	0.80	3.0% (40/1313)	2.5% (17/677)	0.50
Stent/Scaffold Thrombosis (Def/Prob)	3.2% (13/405)	1.4% (3/219)	0.17	0.8% (7/894)	0.4% (2/456)	0.73	1.5% (20/1301)	0.7% (5/675)	0.13

*Not pre-specified and not adjusted for multiplicity

Subgroup Analysis Stratified by RVD of 2.25 mm for All Diabetes Mellitus Subjects

The 1-year rates of TLF, non-hierarchically assessed cardiac death, TV-MI and ID-TLR, and stent / scaffold thrombosis for the all DM subgroup, all DM with RVD ≥ 2.25 mm subgroup and all DM with RVD < 2.25 mm subgroup are shown in **Table 5.2.2-18**. For the all DM with RVD ≥ 2.25 mm subgroup, the observed clinical event rates in the Absorb and Xience arms were lower than in the all DM subgroup, and much lower than in the all DM with RVD < 2.25 mm subgroup. An example is device thrombosis at 1 year, where the rates in Absorb and XIENCE arms of the all DM with all RVD ≥ 2.25 mm subgroup (1.3% vs. 0.6%) were lower compared to all diabetics (3.2% vs. 1.4%) and substantially lower than in the all DM with RVD < 2.25 mm subgroup (10.6% vs. 4.4%).

When compared to all thrombosis events in the ITT population of ABSORB III, the proportion occurring in very small vessel diabetic subjects is noteworthy. Of the 20 occurrences of thrombosis through 1 year for the Absorb arm in the overall ITT population, 45.0% (9/20) were in the all DM with RVD < 2.25 mm subgroup. Of the 5 occurrences of thrombosis in the Xience arm in the ITT population, 40.0% (2/5) were in the all DM with RVD < 2.25 mm subgroup. Therefore, in both device arms there were higher observed rates of thrombosis in diabetic subjects with very small vessels. Data must be taken into perspective given the small sample size of this analysis.

Table 5.2.2-18 Subgroup Information and 1-Year Clinical Outcomes Stratified by Diabetic Status and Core Laboratory Assessed RVD – Per-Subject Analysis (Primary Analysis Group, Intent-to-Treat Population, Per Protocol MI Definition)

	All DM			All DM with RVD ≥ 2.25 mm*			All DM with RVD < 2.25 mm		
	Absorb (N=416)	**XIENCE (N=224)**	**P-value****	**Absorb (N=325)**	**XIENCE (N=177)**	**P-value****	**Absorb (N=88)**	**XIENCE (N=45)**	**P-value****
TLF	10.7% (44/411)	9.1% (20/220)	0.52	7.2% (23/321)	7.5% (13/174)	0.90	23.9% (21/88)	15.6% (7/45)	0.27
Cardiac Death	0.5% (2/411)	0.0% (0/220)	0.55	0.3% (1/321)	0.0% (0/174)	1.00	1.1% (1/88)	0.0% (0/45)	1.00
TV- MI	9.0% (37/411)	7.3% (16/220)	0.46	6.2% (20/321)	6.9% (12/174)	0.77	19.3% (17/88)	8.9% (4/45)	0.12
ID-TLR	5.6% (23/411)	3.6% (8/220)	0.28	3.4% (11/321)	1.1% (2/174)	0.15	13.6% (12/88)	13.3% (6/45)	0.96
Stent/Scaffold Thrombosis (Def/Prob)	3.2% (13/405)	1.4% (3/219)	0.17	1.3% (4/318)	0.6% (1/173)	0.66	10.6% (9/85)	4.4% (2/45)	0.33

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

**Not pre-specified and not adjusted for multiplicity

Subgroup Analysis Stratified by RVD of 2.25 mm for All Non-Diabetes Mellitus Subjects

The 1-year rates of TLF, non-hierarchically assessed cardiac death, TV-MI and ID-TLR, and stent/scaffold thrombosis for the all non-DM subgroup, all non-DM with RVD ≥ 2.25 mm subgroup and all non-DM with RVD < 2.25 mm subgroup are shown in **Table 5.2.2-19**. For both Absorb and Xience, the observed event rates did not show substantial differences between the all non-DM subgroup, the all non-DM with RVD ≥ 2.25 mm subgroup and the all non-DM with RVD < 2.25 mm subgroup. The observed differences in event rates between study arms were consistent across subgroups. There were no statistically significant differences between device arms.

Table 5.2.2-19 Subgroup Information and 1-Year Clinical Outcomes Stratified by Non-Diabetic Status and Core Laboratory Assessed RVD – Per-Subject Analysis (Primary Analysis Group, Intent-to-Treat Population, Per Protocol MI Definition)

	All Non-DM			All Non-DM with RVD ≥ 2.25 mm			All Non-DM with RVD < 2.25 mm		
	Absorb (N=904)	XIENCE (N=462)	P-value**	Absorb (N=748)	XIENCE (N=372)	P-value**	Absorb (N=153)	XIENCE (N=88)	P-value**
TLF	6.3% (57/900)	4.6% (21/457)	0.19	6.4% (48/745)	4.6% (17/368)	0.22	5.9% (9/152)	4.5% (4/88)	0.77
Cardiac Death	0.7% (6/900)	0.2% (1/457)	0.43	0.7% (5/745)	0.3% (1/368)	0.67	0.7% (1/152)	0.0% (0/88)	1.00
TV- MI	4.6% (41/900)	3.3% (15/457)	0.27	4.7% (35/745)	3.5% (13/368)	0.37	3.9% (6/152)	2.3% (2/88)	0.71
ID-TLR	1.8% (16/900)	2.0% (9/457)	0.80	1.7% (13/745)	1.6% (6/368)	0.89	2.0% (3/152)	3.4% (3/88)	0.67
Stent/Scaffold Thrombosis (Def/Prob)	0.8% (7/894)	0.4% (2/456)	0.73	0.7% (5/739)	0.5% (2/367)	1.00	1.3% (2/152)	0.0% (0/88)	0.53

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

** Not pre-specified and not adjusted for multiplicity

A key finding of the subgroup analyses summarized in **Table 5.2.2-18** and **Table 5.2.2-19** is that for subjects treated with Absorb in appropriately sized vessels, the clinical outcomes in diabetics do not differ appreciably from outcomes in non-diabetics. This can be seen in the comparison between Absorb TLF rates (7.2% vs. 6.4%) and Absorb thrombosis rates (1.3% vs. 0.7%) in the all DM with RVD ≥ 2.25 mm and all Non-DM with RVD ≥ 2.25 mm subgroups, respectively.

These findings are consistent with the RVD analysis conducted on the overall population. The outcomes in the diabetic and the non-DM populations when closely aligned with the label (2.5-3.75 mm RVD) also provide evidence that when the Absorb is placed in the appropriately sized vessels, the differences between the two arms are minimal. These findings have important implications on the labeling of the device and physician education, which will be discussed further in **Section 8.0**.

Comparison to Cardiac Death Historical Results

The small observed differences in cardiac death between two arms are not considered to be device related. The cardiac death rate of 0.6% for Absorb is comparable to historical rates

between 0.4% and 0.9 % for Xience and other DES in recent trials with similar subject populations [5-9, 66] while the Xience rate of 0.1% is low compared to the historical rates, which are listed as follows:

- Xience: 0.8%, 0.4%, 0.9% and 0.7% observed in the SPIRIT III (N = 655), SPIRIT IV (N = 2458), XIENCE V USA trials (N = 1839) and PLATINUM trials (N = 762) respectively
- TAXUS: 0.9%, 0.4% and 0.5% in the SPIRIT III (N = 321), SPIRIT IV (N = 1229) and ENDEAVOR IV (N = 775) trials, respectively
- Endeavor ZES: 0.5% in the ENDEAVOR IV (N = 773) trial
- PROMUS Element: 0.9% and in the PLATINUM trial (N = 768)
- PROMUS Element Plus: 0.9% in the EVOLVE II trial (N = 838)
- SYNERGY: 0.5% in the EVOLVE II trial (N = 846)

These studies support that in ABSORB III the cardiac death rate for Xience came in very low as compared to past performance and the rate for Absorb was similar to other DES trials.

Summary of Safety and Effectiveness

To summarize the safety and effectiveness results from the ABSORB III trial, Absorb was non-inferior to Xience for TLF at 1 year. There were small observed differences but no statistically significant 1 year differences between the two devices in all-cause or cardiac mortality, in peri-procedural MI, TV-MI or all MI, and device thrombosis. With regard to effectiveness, statistical significance was not observed for the powered secondary endpoints of ID-TVR, revascularization, or angina but the rates were both low and comparable. In making a decision on safety and effectiveness, it is pertinent to note that in appropriately sized vessels (2.5-3.75 mm RVD), Absorb performs similar to Xience with low and comparable rates. Abbott Vascular is committed to a robust and comprehensive physician education program (described in **Section 8.0**) to ensure the safe use of this device within this indicated population.

5.3 ABSORB III Trial Conclusions

Absorb met its primary endpoint and was comparable with best-in-class Xience for safety and effectiveness as defined by TLF at 1 year. This satisfies the regulatory standard for DES approval by demonstrating a reasonable assurance of safety and effectiveness. There were no statistical differences between Absorb and Xience for safety and effectiveness. The strong results of ABSORB III trial were achieved with the first ever use of Absorb by US physicians in which the median use per investigator was 2 devices. The results were consistent across multiple subgroups with no significant interaction p-values. No significant differences were present in the components of TLF or other measures of safety or effectiveness. There were observed differences present that were further evaluated to gain an understanding of these differences. It was identified that a reference vessel diameter $\geq$ 2.25 mm comprised 81.2% of

subjects and showed smaller difference in event rates between Absorb and Xience for most outcome measures than in the overall population. Abbott Vascular will add appropriate warning and precaution in the labeling, and institute robust physician education program to avoid placement of Absorb in very small vessels which will be used to support further improvement in results. Overall it is concluded that Absorb is comparable to the best-in-class Xience for safety and effectiveness.

5.4 Pharmacokinetic Analysis

Everolimus elution from the Absorb scaffold post-implantation was evaluated in a pharmacokinetic (PK) sub-study, which is part of the ABSORB III clinical trial design. The results show that, similar to Xience, the levels of everolimus eluted from the scaffold are low and transient. Hence, this limits the risk associated with systemic exposure and Absorb's PK profile is considered safe.

A total of 12 subjects who received only Absorb scaffolds at two investigational sites in the US were registered in the PK sub-study. All subjects had single target lesions that were treated with only Absorb. The number of scaffolds implanted per subject was one or two. The total dose of everolimus received by the subjects ranged from 181 to 443 µg. **Table 5.4-1** provides whole blood everolimus PK parameters determined from the subjects receiving Absorb. Pharmacokinetic parameters obtained after oral dosing of everolimus in renal transplant patients are provided in **Table 5.4-2** as a comparison.

Table 5.4-1 Pharmacokinetic Results of Everolimus after Implantation of at Least One Absorb (Individual Dose Ranged from 181 µg - 443 µg)

Pharmacokinetics of Everolimus	ABSORB III PK Sub-Study
N	12
Stents/Scaffolds used	1 - 2
Dose (µg)	181 - 443
C_{max} (ng/mL)	1.085 - 4.460
AUC_{last} (ng*h/mL)	25.37 - 104.6
T_{max} (h)	0.17 - 2.37
$t_{1/2}$ (h)	45.9 - 115

N = number of subjects. Range is provided for dose and PK parameters (Cmax, AUClast, Tmax, t1/2).

Table 5.4-2 Pharmacokinetics Parameters after Oral Dosing of Everolimus in Renal Transplant Patients

Everolimus Oral Dose**	C_{max} (ng/mL)	AUC (ng.h/mL)
0.5 mg/d BID	5.0 ± 2.9	34 ± 23 ($AUC_{12)}$
1 mg/d BID	11.6 ± 4.4	81 ± 34 ($AUC_{12)}$
2 mg/d BID	21.9 ± 10.5	164 ± 78 ($AUC_{12)}$

BID, twice per day
**Oral dosing data presented at steady state (7 days)

Everolimus blood concentrations were low but could be quantified up to 168 hours after implantation of the last Absorb scaffold. Although short-lived, individual C_{max} values (1.085 to 4.460 ng/mL) were slightly higher than the minimum systemic, chronically maintained therapeutic level of ≥ 3.0 ng/mL necessary to be effective for prevention of organ rejection [67, 68]. Blood concentrations were below 3.0 ng/mL in all subjects by 4 hours after the last scaffold deployment. The rapid disappearance of everolimus after implantation of the Absorb scaffold further limits the systemic extent of exposure. Therefore, everolimus blood concentrations seen with the Absorb scaffold are considered safe.

The pharmacokinetic profile for everolimus eluted from the Absorb scaffold has adequately been characterized and is consistent with previous clinical and nonclinical data. The PK characteristics of everolimus after deployment of the Absorb scaffold (dose range: 181 to 443 µg) were shown to be predictable due to dose-proportional behavior. The local arterial delivery and limited systemic exposure provide the opportunity for successful treatment of coronary lesions with limited risk associated with systemic exposure. The pharmacokinetic profiles seen with the Absorb scaffold are considered to be safe.

6.0 Supportive Clinical Studies Conducted Outside of the United States

Key Points

- The ABSORB family of clinical trials (ABSORB II, ABSORB Japan, ABSORB EXTEND and ABSORB Cohort B) further support safety and efficacy of Absorb at 1 year.
- ABSORB II and ABSORB Japan both randomized trials, showed no statistical difference in 1 year TLF between Absorb and Xience:
    - ABSORB II: 4.8% Absorb vs. 3.0% Xience, p = 0.35
    - ABSORB Japan: 4.2% Absorb vs. 3.8% Xience, p = 0.85
- Long-term data from earlier trials with Absorb provides supporting information that after 1 year, Absorb accrues either similar or less TLF/MACE rates compared to XIENCE

Principal safety and effectiveness information for the Absorb is derived from the ABSORB III trial. However, there is also worldwide data available from the ABSORB family of clinical trials, supporting the safety and effectiveness of Absorb. These trials include ABSORB II, ABSORB Japan, ABSORB EXTEND, and ABSORB Cohort B, all of which evaluated Absorb performance in subjects with ischemic heart disease caused by *de novo* lesions in native coronary arteries. A summary of the design of these four trials is provided below in **Table 6.0-1**. As described in the following subsections, these studies show consistency with 1 year ABSORB III safety and effectiveness, supportive long-term clinical evidence, and data demonstrating return of physiologic function and late lumen enlargement.

Table 6.0-1 ABSORB Family of Clinical Trials Conducted Outside the US: Trial Designs

	ABSORB Cohort B	ABSORB EXTEND	ABSORB II	ABSORB JAPAN
Trial Design	Multi-center Non-randomized Single Arm First-in-man	Multi-center Non-Randomized Single Arm Continued Assessment	Multi-center Randomized (2:1) Single-blinded Active-Control	Multi-center Randomized (2:1) Single-blinded Active-Control
Numbers of Subjects	N = 101 (all Absorb) - Group B1: 45 - Group B2: 56	N = 812 (all Absorb)	N = 501 - Absorb: 335 - Xience Control: 166	N = 400 - Absorb: 266 - Xience Control: 134
Vessel Sizes and Lesion Lengths	RVD: 3.0 mm Length: ≤ 14 mm	D_{max} ≥ 2.0 mm and D_{max} ≤ 3.3 mm Length: ≤ 28 mm	D_{max} ≥ 2.25 mm and ≤ 3.8 mm Length: ≤ 48 mm	D_{max} ≥ 2.25 mm and ≤ 3.75 mm, Length: ≤ 24 mm
Clinical follow-ups	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 schedule	Group 1: 180 days, 2 years and 5 years (N = 45) Group 2: 1 year, 3 years, and 5 years (N = 6)	Post-procedure and 2 years*	3 years	13 months, 2 to 4 years*
IVUS and/or OCT Follow-up Schedule	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*	3 years	3 years

*imaging sub-groups

6.1 One-Year Clinical Outcomes in Absorb Trials Outside the US (OUS)

One year clinical outcome data supporting ABSORB III trial results are available from ABSORB II, ABSORB Japan, ABSORB EXTEND, and ABSORB Cohort B. In those four trials, target lesion failure (or MACE in the case of ABSORB Cohort B) at 1 year ranged from 4.2% to 6.9% for Absorb and the definite/probable scaffold thrombosis rate ranged from 0 % to 1.5%. Additionally, in ABSORB II and ABSORB Japan, the event rates were not statistically different between the Absorb and the Xience arms.

Table 6.1-1, below, provides key baseline subject characteristics for each of those four OUS trials. **Table 6.1-2** provides key 1-year clinical outcomes for each trial. In both tables, ABSORB III data were added as a comparison.

Table 6.1-1 ABSORB Family of Clinical Trials Conducted Outside the US: Key Subject Characteristics

	ABSORB II		ABSORB Japan		ABSORB EXTEND	ABSORB Cohort B	ABSORB III	
	Absorb (N=335)	Xience (N=166)	Absorb (N=266)	Xience (N=134)	Absorb (N=812)	Absorb (N=101)	Absorb (N=1322)	Xience (N=686)
Age (year)	61.5 ± 10	60.9 ± 10	67.1 ± 9.4	67.3 ± 9.6	61.1 ± 10.8	62.3 ± 8.9	63.5 ± 10.6	63.6 ± 10.3
Male Subjects	75.5%	79.5%	78.9%	73.9%	74.3%	72.3%	70.7%	70.1%
Current Tobacco Use	23.6%	21.7%	19.9%	21.6%	23.2%	17.0%	21.3%	20.7%
Any Diabetes Mellitus	23.9%	24.1%	36.1%	35.8%	26.5%	16.8%	31.5%	32.7%
Hypertension	69.0%	71.7%	78.2%	79.9%	71.4%	66%	84.9%	85.0%
Dyslipidemia	75.2%	80.1%	82.0%	82.1%	71.9% (hypercholesterolemia)	85.1% (hypercholesterolemia)	86.2%	86.3%
Family History of premature CAD	36.6%	41.3%	6.5%	8.1%	36.7%	54.6%	49.3%	49.8%
Prior MI	28.0%	28.9%	16.0%	23.9%	28.5%	25.0%	21.5%	22.0%
Stable Angina	63.9%	64.5%	63.9%	65.7%	56.8%	68.3%	57.3%	60.8%
Unstable Angina	20.3%	22.3%	9.8%	16.4%	26.5%	14.9%	26.9%	24.5%

Table 6.1-2 ABSORB Family of Clinical Trials Conducted Outside the US: Key Outcomes at 1 Year

	ABSORB II		ABSORB Japan		ABSORB EXTEND	ABSORB Cohort B	ABSORB III	
	Absorb (N=335)	Xience (N=166)	Absorb (N=266)	Xience (N=134)	Absorb (N=812)	Absorb (N=101)	Absorb (N=1322)	Xience (N=686)
COMPOSITE EFFECTIVENESS AND SAFETY								
TLF	4.8%	3.0%	4.2%	3.8%	5%	6.9% (MACE)	7.8%	6.1%
EFFECTIVENESS								
Ischemia-Driven TLR	1.2%	1.8%	2.6%	2.3%	2.3%	4.0%	3.0%	2.5%
TLR, CABG	0.0%	0.0%	0.0%	0.0%	0.2%	0.0%	0.2%	0.4%
TLR, PCI	1.2%	1.8%	2.6%	2.3%	2.1%	4.0%	2.8%	2.2%
Ischemia-Driven TVR	1.8%	3.6%	4.9%	3.8%	2.8%	4.0%	5.0%	3.7%
SAFETY								
All Death	0.0%	0.6%	0.8%	0.0%	1.1%	-	1.1%	0.4%
Cardiac Death	0.0%	0.0%	0.0%	0.0%	0.7%	0.0%	0.6%	0.1%
Vascular Death	0.0%	0.0%	0.4%	0.0%	0.1%	-	0.2%	0.0%
Non-cardiovascular Death	0.0%	0.6%	0.4%	0.0%	0.2%	-	0.4%	0.3%
TV-MI	4.2%	1.2%	3.4%	2.3%	3.3%	-	6.0%	4.6%
QMI	0.6%	0.0%	1.1%	0.0%	1.0%	-	0.7%	0.3%
NQMI	3.6%	1.2%	2.3%	2.3%	2.3%	-	5.3%	4.3%
All MI	4.5%	1.2%	3.4%	2.3%	3.3%	3.0%	6.9%	5.6%
QMI	0.6%	0.0%	1.1%	0.0%	1.0%	0.0%	0.8%	0.4%
NQMI	3.9%	1.2%	2.3%	2.3%	2.3%	3.0%	6.1%	5.2%
Cumulative ARC-defined Definite + Probable Stent/Scaffold Thrombosis (0-393 days)	0.9%	0.0%	1.5%	1.5%	1.0%	0.0%	1.54%	0.74%

6.2 Two-Year Data from ABSORB II, ABSORB EXTEND, and ABSORB Cohort B Trials

As detailed in the executive summary the ABSORB III trial was designed to establish non-inferiority in 1 year TLF comparing Absorb to Xience. In addition, clinical data on Absorb after 1 year can also be used to support the evaluation of the device. Currently two year data is available from the ABSORB Cohort B, ABSORB EXTEND and ABSORB II trials. In addition, data out to 3 and 5 years is also available on the ABSORB EXTEND and Cohort B trials, respectively.

The ABSORB Cohort B, ABSORB EXTEND, and ABSORB II trials enrolled similar subjects to ABSORB III. Cohort B and ABSORB EXTEND were single arm trials, and ABSORB II was the first randomized trial comparing Absorb to Xience, at 46 sites across Europe and New Zealand. The ABSORB II trial was not powered for clinical outcomes; the primary endpoint consists of quantitative measures of minimum lumen diameter and vasomotion at 3 years.

Table 6.2-1 below presents TLF rates at 1 and 2-year for each of these trials and **Table 6.2-3** presents stent / scaffold thrombosis (ST) rates. When pooling data from the 1248 subjects in these three ABSORB trials, which all use the same MI definition (WHO definition), the average increase in TLF rate from 1 to 2-year was 2% for Absorb. To put these data into perspective the increase in TLF rate between 1 and 2-year for Xience in the SPIRIT III trial was also 2% (**Table 6.2-2**).

Regarding ST thrombosis, the average increase in ST rate for Absorb between 1 and 2-year was 0.5% (**Table 6.2-3**) and it should be noted that there was no scaffold thrombosis event in the Cohort B trial. As a comparison, in the SPIRIT III trial, the increase in ST rate for Xience between 1 and 2-year was 0.4 % (**Table 6.2-4**).

Table 6.2-1 ABSORB Family of Clinical Trials Conducted Outside the US: Absorb TLF Rates at 1 and 2 Years (MI per WHO definition)**

	N	Year 1	Year 2	Difference [95% CI]
Cohort B*	101	6.9% (7/101)	9.0% (9/100)	2.07% [-5.41%, 9.55%]
ABSORB EXTEND	812	5.1% (41/811)	6.9% (56/807)	1.88% [-0.43%, 4.20%]
ABSORB II	335	4.8% (16/331)	7.0% (23/328)	2.18% [-1.42%, 5.78%]
Pooled	1248	5.1% (64/1243)	7.1% (88/1235)	1.98% [0.09%, 3.87%]

* MACE (Major Adverse Cardiac Events: cardiac death, MI, and ID-TLR) used instead of TLF.
** WHO definition of MI: Q wave MI defined as new pathological Q wave on the ECG; Non-Q wave MI defined as elevation of CK level to ≥ 2 times ULN with elevated CK-MB in the absence of pathological Q-waves.

Table 6.2-2 Xience V (SPIRIT III trial) TLF Rates at 1 and 2 Years*

	N	Year 1	Year 2	Difference [95% CI]
Xience V (SPIRIT III)	669	5.5% (36/657)	7.5% (48/643)	1.99% [-0.69%, 4.66%]

* WHO definition of MI: Q wave MI defined as new pathological Q wave on the ECG; Non-Q wave MI defined as elevation of CK level to ≥ 2 times ULN with elevated CK-MB in the absence of pathological Q-waves.

Table 6.2-3 ABSORB Family of Clinical Trials Conducted Outside the US: Absorb Stent / Scaffold Thrombosis Rates at 1 and 2 Years

	N	Year 1	Year 2	Difference [95% CI]
Cohort B	101	0.0% (0/101)	0.0% (0/100)	0.00% [0.00%, 0.00%]
ABSORB EXTEND	812	1.0% (8/808)	1.5% (12/799)	0.51% [-0.57%, 1.60%]
ABSORB II	335	0.9% (3/329)	1.5% (5/325)	0.63% [-1.06%, 2.31%]
Pooled	1248	0.9% (11/1238)	1.4% (17/1224)	0.50% [-0.34%, 1.34%]

Table 6.2-4 Xience V (SPIRIT III Trial) Stent Thrombosis Rates at 1 and 2 Years

	N	Year 1	Year 2	Difference [95% CI]
Xience V (SPIRIT III)	669	0.9% (6/650)	1.3% (8/630)	0.4% [-0.80%, 1.49%]

6.3 Absorb Clinical Data beyond 2 years from ABSORB Cohort B and ABSORB EXTEND Trials

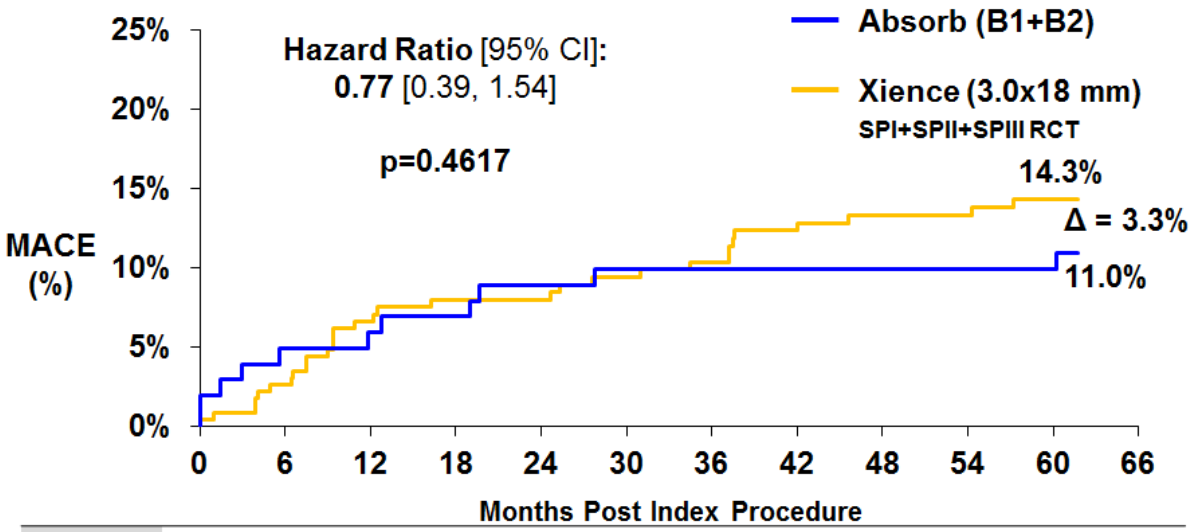
Longer-term clinical data are available out to 5 years for all ABSORB Cohort B subjects, and out to 3 years for a subset of ABSORB EXTEND subjects. The clinical outcomes from the Cohort B trial, presented in **Table 6.3-1**, below, show continued safety and effectiveness of Absorb beyond 1 and 2 years. In the ABSORB Cohort B trial, the MACE rate was 6.9% at 1 year and 11% at 5 year, which represents an average annual increase of 1% between 1 and 5 years. Only one MACE event (due to TLR) was reported between 3 and 5 years, and no MI, cardiac death or scaffold thrombosis were reported between 1 and 5 years.

Table 6.3-1 Key Clinical Outcomes of ABSORB Cohort B (ITT Population) through 5 Years

	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 EFFECTIVENESS AND SAFETY					
MACE	6.9% (7/101)	9.0% (9/100)	10.0% (10/100)	10.0 (10/100)	11.0 (11/100)
EFFECTIVENESS					
Ischemia-Driven TLR	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% (0/100)	0.0% (0/100)	0.0% (0/100)	0.0% (0/100)
TLR, PCI	4.0% (4/101)	6.0% (6/100)	7.0% (7/100)	7.0% (7/100)	8.0% (8/100)
Ischemia-Driven TVR	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% (0/100)	0.0% (0/100)	0.0% (0/100)	0.0% (0/100)
All MI	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% (0/100)	0.0% (0/100)	0.0% (0/100)	0.0% (0/100)
NQMI	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% (0/99)	0.0% (0/97)	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 ± 28 days; 3 year ± 28 days; 4 year ± 28 days; 5 year ± 28 days

Figure 6.3-1, below, shows a comparison of MACE rates between Absorb (Cohort B trial, full cohort) and historical Xience (227 subjects from SPIRIT I, II and III randomized controlled trials receiving 3.0 x 18 mm stent) out to 5 years. The MACE rate for Absorb remained stable between 3 and 5 years; whereas, event rates continued to increase for Xience beyond 3 years. At 5 years the difference in MACE rate between Absorb and Xience was 3.3%. Granted this is a post-hoc comparison using historical Xience data, the outcomes support that over time the event rates associated with Absorb may accrue similar or less than metallic DES. The ABSORB IV randomized trial data will further confirm these findings.

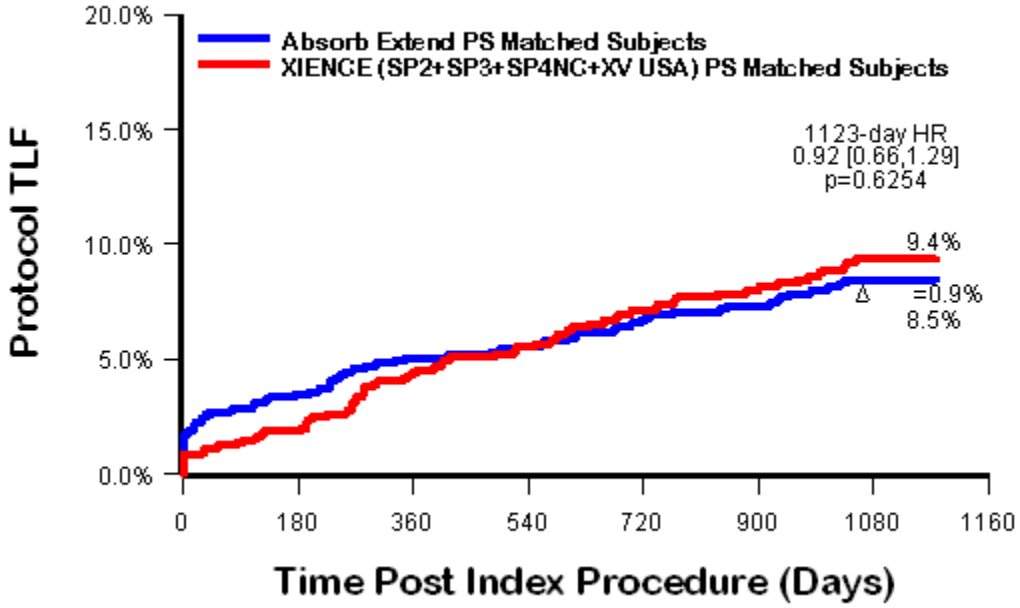


Time after index (d)	0	37	194	284	393	573	758	1123	1488	1853
Absorb	101	99	96	96	94	92	91	88	86	85
Xience	227	224	219	211	204	202	191	182	174	169

Figure 6.3-1 Kaplan-Meier Estimates of Cumulative MACE rates of the ABSORB Cohort B (blue, N = 101) and the 227 Subjects Receiving Single 3.0×18 mm Xience in the SPIRIT I, II and III Trials (yellow) [69]

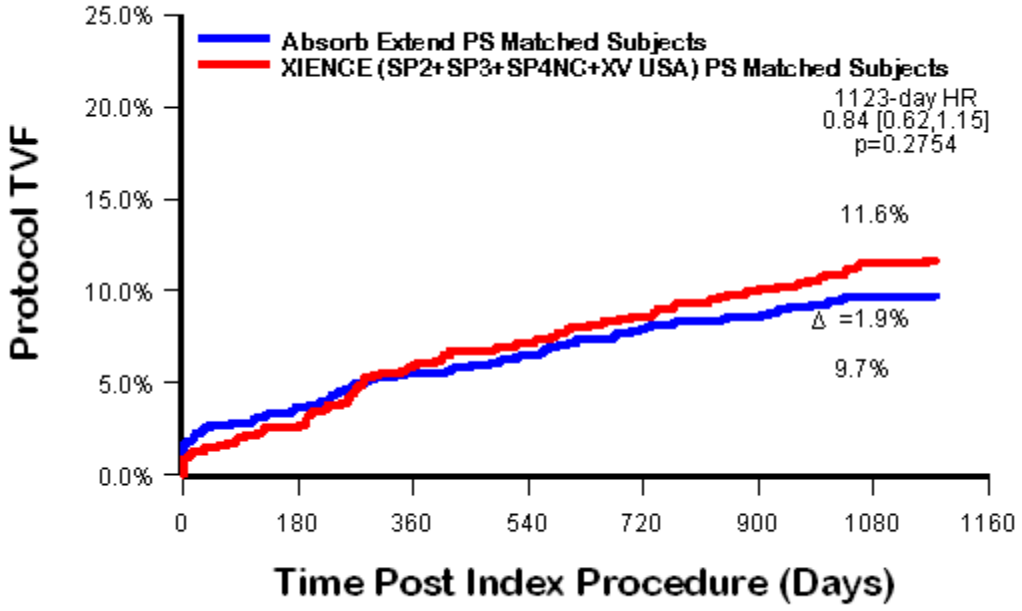
Figure 6.3-2 below presents a propensity matched analysis for the endpoint of TLF for Absorb in ABSORB EXTEND compared to Xience in XIENCE V USA/SPIRIT II/SPIRIT III/SPIRIT IV trials. Propensity score analysis is an acceptable statistical method to adjust baseline characteristics to create a better match between both arms and hence reduce bias in outcomes. Between 1 and 2 years, the Absorb and Xience TLF curves start to cross and by 3 years the Absorb TLF rate is 8.5% as compared to 9.4% for Xience. **Figure 6.3-3** presents a propensity matched analysis of TVF (target vessel failure: composite of cardiac death, all MI and ischemia-driven target lesion revascularization) for Absorb versus Xience. Just like TLF, the TVF event rates are slightly higher for Absorb during the first year; but around 1 year the Kaplan-Meier curves for Absorb and Xience start to cross. Therefore, by 3 years, the TVF rate is lower for Absorb compared to Xience (9.7% vs 11.6%). Regarding scaffold

thrombosis in ABSORB EXTEND, the increase for Absorb between 2 and 3 years was 0.5%, similar to the 0.5% increase observed between 1 and 2 years. As explained above, this is a post-hoc comparison using historical Xience data, and the outcomes support that over time the event rates associated with Absorb may accrue similar or less than metallic DES. The ABSORB IV randomized trial data will further confirm these findings.



			Number of subjects at risk			
Time after index procedure (days)	0	37	194	393	758	1123
Absorb	812	790	782	766	740	566
Xience	812	798	773	710	623	596

Figure 6.3-2 Kaplan-Meier Curve Representing the Estimated Cumulative Incidence Rates of TLF to 1123 Days; ABSORB EXTEND vs. Xience V (SPIRIT II, III and IV Non-Complex Subjects + XIENCE V USA); Propensity Matched



	Number of subjects at risk					
Time after index procedure (days)	0	37	194	393	758	1123
Absorb	812	790	780	762	730	559
Xience	812	795	766	699	611	580

Figure 6.3-3 Kaplan-Meier Curve Representing the Estimated Cumulative Incidence Rates of TVF to 1123 days; ABSORB EXTEND vs. Xience V (SPIRIT II, III and IV Non-Complex Subjects + XIENCE V USA); Propensity Matched

In conclusion, based on the data available from 1248 subjects from the three ABSORB trials presented above, the incremental rates of TLF (or MACE) and stent/scaffold thrombosis between 1 and 2 years are similar between Absorb and Xience. In addition, preliminary data with Absorb after 2 years suggest that relatively few events accrue after 2 to 3 years.

6.4 Evidence for Anatomic and Physiologic Vessel Restoration from the ABSORB Cohort B Trial

In addition to providing support for long-term safety and effectiveness of Absorb, the ABSORB Cohort B trial provides imaging analyses that demonstrate the potential additional benefits of Absorb: late lumen expansion, no permanent implant left behind as evidenced by OCT data, and return of vasomotor function. These observations demonstrate that, as the

scaffold resorbs, the vessel is able to vasodilate in response to vasodilators and shows a more normal neointimal lining. In addition, the non-invasive imaging technique of MSCT can be used to visualize restenosis because the blooming effect observed with metallic stent does not occur with Absorb.

6.4.1 ABSORB Cohort B Intravascular Ultrasound (IVUS) Outcomes

Late lumen enlargement is a unique feature of Absorb, which is not seen with metallic stents because the vessel is constricted and unable to undergo adaptive remodeling. The increase in vessel diameter is reminiscent of what is seen in long-term follow-up with balloon angioplasty [70], and contributes to keeping the vessel patent overtime.

As presented in **Table 6.4.1-1**, below, IVUS measurements from the ABSORB Cohort B trial demonstrate late lumen enlargement as evidenced by a significant increase in mean lumen area and scaffold area from 6 months to 2 years, and 6 months to 5 years, in Group B1 and from 1 to 3 years in Group B2. The mean lumen area increased from 6.59 ± 1.20 mm^2 to 7.24 ± 1.91 mm^2 ($p = 0.015$) between 6 months and 2 years in Group B1, and from 6.31 ± 1.01 mm^2 to 6.70 ± 1.48 mm^2 ($p = 0.0028$) between 1 and 3 years in Group B2.

Along with an increase in lumen area, the average scaffold area also increased from 6.63 ± 1.16 mm^2 to 7.52 ± 1.79 mm^2 ($p < 0.0001$) between 6 months and 2 years in Group B1, and from 6.37 ± 0.97 mm^2 to 7.05 ± 1.39 mm^2 ($p < 0.0001$) between 1 and 3 years in Group B2. Scaffold area cannot be assessed at 5 years because the scaffold has fully resorbed and struts are no longer visible (see **Section 6.4.2**).

Table 6.4.1-1 Paired IVUS through 5 Years (ABSORB Cohort B, ITT population)

	Post-Procedure	6 Month	1 Year	2 Year	3 Year	5 Year	p-value (6m vs 2Y)*	p-value (6m to 5Y)*	p-value (1Y vs 3Y)*	p-value (1Y vs 5Y)*
Average Lumen Area (mm^2)										
Group B1 (L=21)	6.75 ± 1.19	6.59 ± 1.20	-	7.24 ± 1.91	-	7.46 ± 2.45	0.0153	0.0215	-	-
Group B2 (L=30*)	6.31 ± 0.86	-	6.31 ± 1.01	-	6.70 ± 1.48	6.48 ± 1.50	-	-	0.0028	0.4378
Average Scaffold area (mm^2)										
Group B1 (L=21)	6.75 ± 1.19	6.63 ± 1.16	-	7.52 ± 1.79	-	NA	< 0.0001	NA	-	-
Group B2 (L=30**)	6.31 ± 0.86	-	6.37 ± 0.97	-	7.05 ± 1.39	NA	-	NA	< 0.0001	NA

Group B1 subjects had IVUS at 6 months, 2 years and 5 years; Group B2 subjects had IVUS at 1 year, 3 years and 5 years.
* 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.
**L=28 at 5 years

In addition to late lumen enlargement, plaque regression has also been demonstrated in ABSORB Cohort B. **Figure 6.4-1,** below, shows serial, paired quantitative IVUS measurements of vessel area, plaque area and mean lumen area. The plaque area represents the scar and underlying plaque formation as the vessel heals itself overtime. Initially, plaque area increases with a peak at 24 months but then starts regressing overtime. Mean lumen area slightly decreases during the first 6 months as the plaque area increases. However, after 6 months, the lumen starts getting larger, despite the fact that the plaque does not start to decrease until 24 months. At 5 years, the lumen is actually larger than it was at baseline. Lumen enlargement is allowed to occur with Absorb because the vessel is uncaged, normal vascular adaptive responses are restored, and the vessel can increase in size to accommodate the plaque.

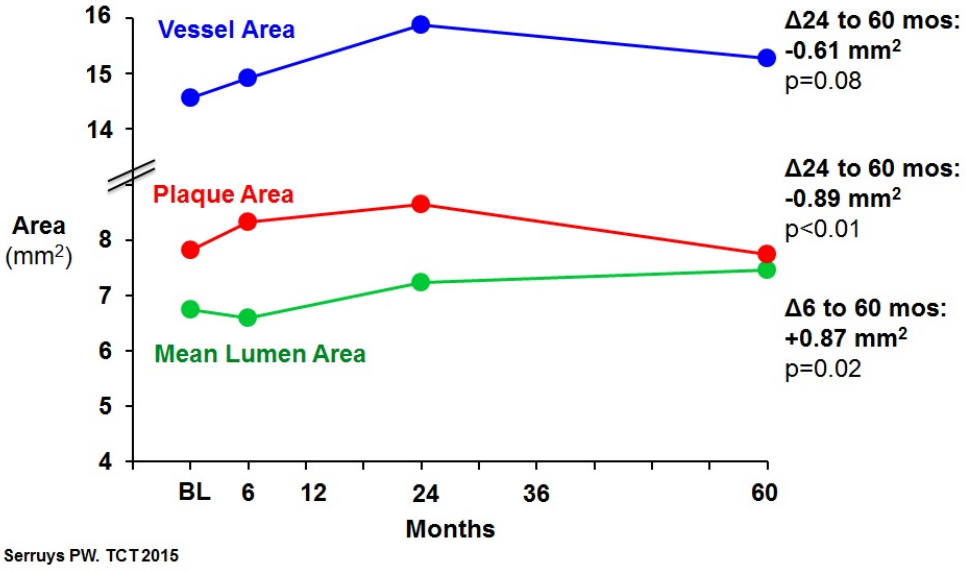


Figure 6.4-1 Serial Paired Quantitative IVUS Measurements (N = 21) from ABSORB Cohort B, Group B1 [69]

6.4.2 ABSORB Strut Healing and Evidence for Long Term Vessel Restoration: ABSORB Cohort B Data

Serial OCT imaging was used to visualize tissue coverage of Absorb struts over time, as well as the resorption of Absorb over a 5-year period. The morphological changes visualized by OCT support the late lumen gain that was identified by the IVUS measurements. Unlike with IVUS, OCT was able to visualize an increase in scaffold area from 6 months to 3 years.

OCT results are presented in **Table 6.4.2-1**, below. Strut coverage was about 98% (1.8% of the struts were uncovered) at 6 months in Group B1 and 97% (3% of the struts were uncovered) at 1 year in Group B2. By 5 years, struts were no longer identifiable in both groups, consistent with complete integration of struts into the arterial wall [71]. These

clinical results are congruent with preclinical observations, demonstrating that over time there is complete stable neointimal coverage and scaffold integration, ultimately yielding a unconstrained, healed artery [72].

Figure 6.4.2-1, below, illustrates the gradual resorption of Absorb over 5 years, and the replacement of the struts by normal-appearing tissue.

Table 6.4.2-1 Paired OCT through 5 Years (ABSORB Cohort B, ITT population)

% Uncovered Struts	Post-Procedure	6 Month	1 Year	2 Year	3 Year	5 Year	p-value (post vs 6m)*	p-value (post vs 1Y)*	p-value (6M to 2Y)*	p-value (1Y to 3Y)*
Group B1 (L=13)	96.97 ± 6.83	1.80 ± 1.63	-	1.40 ± 2.37	-	NA	0.0002	-	0.1909	-
Group B2 (L=17)	97.65 ± 5.56	-	3.03 ± 2.81	-	1.70 ± 1.59	NA	-	< 0.0001	-	0.0131

Group B1 subjects had OCT at 6 months, 2 years and 5 years; Group B2 subjects had IVUS at 1 year, 3 years and 5 years.
* 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.

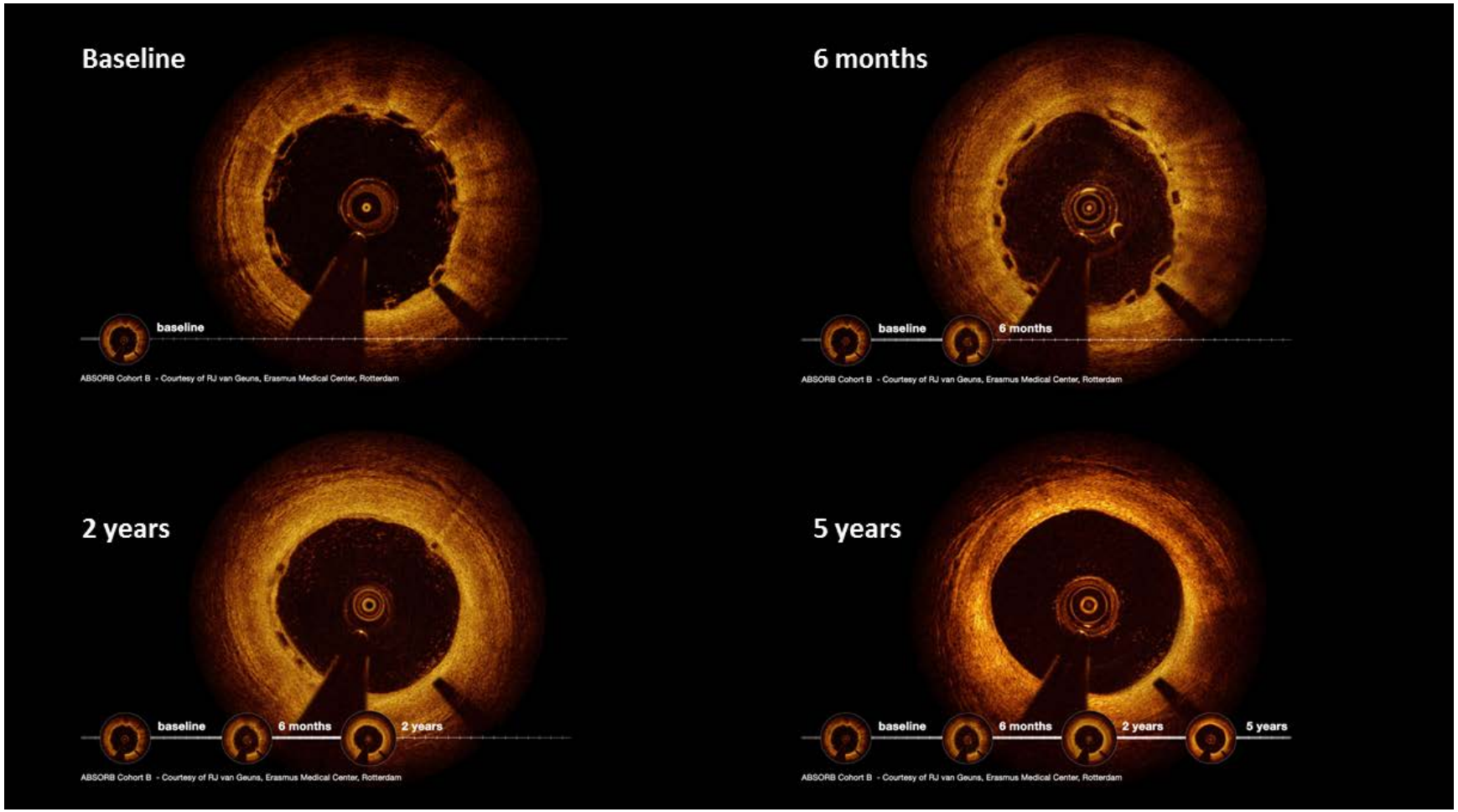


Figure 6.4.2-1 ABSORB Cohort B Subject: OCT Evidence of Complete Scaffold Integration

In ABSORB Cohort B, OCT was also used to conduct an analysis of jailed side branches. A total of 12 jailed side branches were analyzed. **Figure 6.4.2-2** below shows an example of a side branch jailed after the procedure, and becoming unjailed at 5 years after the Absorb scaffold has resorbed [73]. This would be impossible with a metallic stent, which would permanently jail the branch.

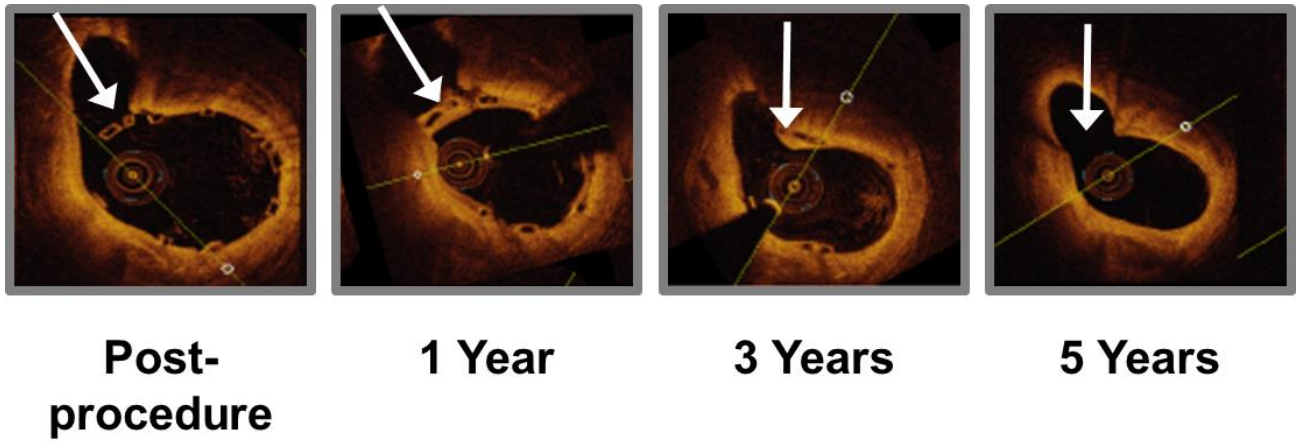


Figure 6.4.2-2 Unjailing of Side Branch with Absorb through 5 Years [74]

6.4.3 ABSORB Cohort B 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 subjects from Group 2 underwent vasomotor function test with nitrate administration (**Table 6.4.3-1**). 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 subjects from the full ABSORB Cohort B (23 from Group 1 and 34 from Group 2) completed vasomotor function tests with nitrate administration (**Table 6.4.3-1**). 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).

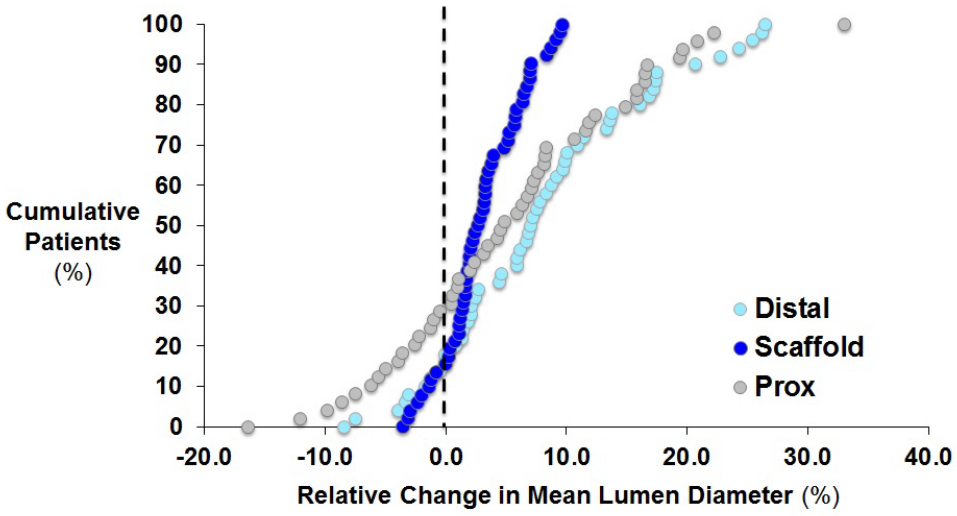
These data indicate that with gradual disappearance of the scaffold the vessel is healing, physiological function is restored and the treated segment is free to move in response to physiological stimuli.

Table 6.4.3-1 Vasomotor Function by Nitroglycerine Injection at 2, 3 and 5 Years (PTE population)**

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

* 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.
** Per-treatment Evaluable population is defined as subjects who have received the clinical investigation device at the target lesion, who have no major procedural protocol deviation, no bailout stenting and for whom follow-up data is available.

A visual representation of vasomotion is presented in **Figure 6.4.3-1**, below. Upon administration of nitrate, the majority of the treated segments display vasodilation, as evidenced by an increase in mean lumen diameter. Importantly, vasodilatation was observed within the scaffolded segment (dark blue dots). Although not performed in this study, vasomotion would not be possible with metallic stent due to permanent caging of the vessel [23].



Serruys PW. TCT 2015
Relative change = 100 x (mean LD post Nit-mean LD pre Nit) / mean LD pre Nit

Note: Shown are relative changes of Mean Lumen Diameter (LD) in the scaffold (dark blue) and in the 5 mm segments proximal (grey) and distal (light blue) to the scaffold, in response to nitrate. A total of 53 lesions were analyzed [69]

Figure 6.4.3-1 Absorb Vasomotion at 5 years in ABSORB Cohort B Trial

6.5 Absorb Multi-Slice Computed Tomography (MSCT) Analysis

Visualization and evaluation of the vessel lumen by MSCT is challenging for vessel segments with a metallic stent, owing to the blooming artifact caused by metallic stent struts. Absorb does not interfere with X-ray penetration since it is made of polymeric material, and thus could potentially allow for a noninvasive method of evaluating vessel stenosis post-stenting. MSCT assessments of Absorb treated vessel segments were evaluated at 18 months in the ABSORB Cohort B trial and 13 months in the ABSORB Japan trial.

In ABSORB Cohort B, it was possible to assess quantitatively the scaffolded segment 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 6.5-1**).

Table 6.5-1 Key MSCT Data from 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

In the MSCT subgroup of the ABSORB Japan trial, the diagnostic capabilities of MSCT with Absorb versus Xience were compared at 13 months post-implantation, and this analysis will also be conducted at 3 years. As shown in **Figure 6.5-1** at 13 months Absorb treated segment shows no blooming whereas a blooming artifact is present within the Xience treated segment [75]. Due to the lack of blooming artifact, a higher percentage of Absorb treated segments were able to be assessed compared to Xience (94.3% vs. 66.7%, p<0.01, respectively).

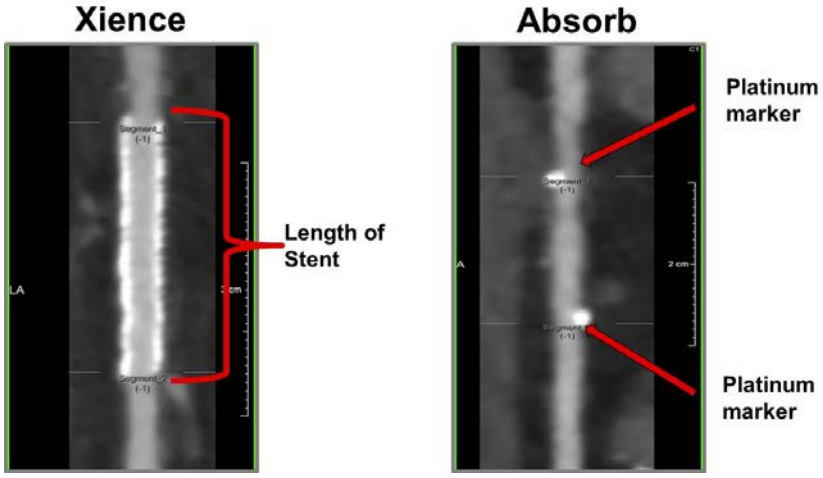


Figure 6.5-1 13 month MSCT Comparing Blooming Artifact Associated with Metallic DES Compared to no Blooming with Absorb due to Polymeric Scaffold [75]

The data from ABSORB Cohort B and ABSORB Japan 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 provide economic benefits.

6.6 Summary

In conclusion, the ABSORB family of clinical trials provides a global perspective of Absorb performance in several different clinical trials. The trial data continues to reinforce Absorb's comparable performance to Xience in the first few years after implantation. In patient populations similar to ABSORB III, Absorb shows consistently low rates of TLF, MACE, and safety and effectiveness endpoints comparable to Xience in the first year (in ABSORB II and ABSORB Japan trials), with emerging data beyond 3 years (Absorb EXTEND and Cohort B) suggesting trends toward better long term outcomes compared to Xience. In addition, imaging results from ABSORB Cohort B replicated what was observed in the animal model showing that by 5 years, all Absorb struts were replaced by normal appearing tissue and the vessel was able to move as evidenced by a significant increase in mean luminal diameter in response to nitroglycerine.

7.0 Continuous Learning

In the ABSORB III trial, the majority of the physicians had little to no experience with Absorb and were implanting the device for the first time. As mentioned prior, the median use of Absorb per ABSORB III investigator was 2 procedures. Nevertheless, the ABSORB III trial met its primary endpoint and Absorb was shown to be non-inferior for the composite safety and effectiveness endpoint of TLF at 1 year. Additionally, when implanted in appropriately sized vessels, Absorb outcomes improved even further.

Absorb BVS received CE mark approval in 2010, is approved in over 100 countries and > 125,000 patients have been treated. Absorb usage outside the US has shown that there is a continuous decline in event rates over time. This is attributed to continued learning from the physicians using Absorb and a focus on optimal Absorb implantation techniques that has resulted in improved clinical outcomes.

This is supported by several trials and registries which identified that use of optimal Absorb techniques was needed to improve clinical outcomes. GHOST-EU [14] was one of the earlier real world registries that provided such insight. The effectiveness outcomes were excellent and in line with expectations with metallic DES, but there was some concern that thrombosis rates were a little higher than expected (1.5% in the first 30 days in early experience) [13, 16]. The rate of scaffold thrombosis after 6 months was very low (0.1%), with an overall 1-year rate of 2% [16]. However, in the GHOST EU trial there was a lack of consistent use of Absorb optimal implantation techniques across sites. The thrombosis events appeared to cluster in the first 30 days, in which it was concluded that there was a need for more accurate lesion selection and use of optimal implantation techniques [16]. Shortly after the publication of the GHOST EU data, many of the physicians participating in the GHOST EU registry published a paper that detailed standard operating protocol for Absorb BVS to serve as practical guidelines for new users of Absorb [76]. These guidelines focused on use of intravascular imaging or use of the pre-dilatation balloon for appropriate

vessel sizing, good lesion preparation and high pressure post-dilatation with a non-compliant balloon.

Since the GHOST EU publication, there have been other subsequent analyses which have demonstrated that optimal Absorb implantation techniques can result in even better clinical outcomes. A recent retrospective propensity analysis from a real world patient registry (single center) showed comparable 6 month MACE rates between Absorb (N = 92) and Xience (N = 92), 3.3% and 7.6%, respectively, and no ST events in either arm [14]. Importantly, the authors noted that key in the successful treatment with Absorb is good lesion preparation, accurate scaffold sizing and liberal performance of high pressure post-dilatation. The use of these techniques was found to be high in the Absorb arm (pre-dilatation 97.8%, IVUS usage for appropriate scaffold sizing was 82.5% and post-dilatation usage was 99.3%).

The 4Cities [15] All Comers Registry is another recent study that reported improved clinical outcomes after implementing an Absorb specific implantation protocol. A comparison of scaffold thrombosis rates before and after the use of the protocol showed a reduction in scaffold thrombosis (**Figure 7.0-1**). It was concluded that ST rates could be reduced when using appropriate techniques.

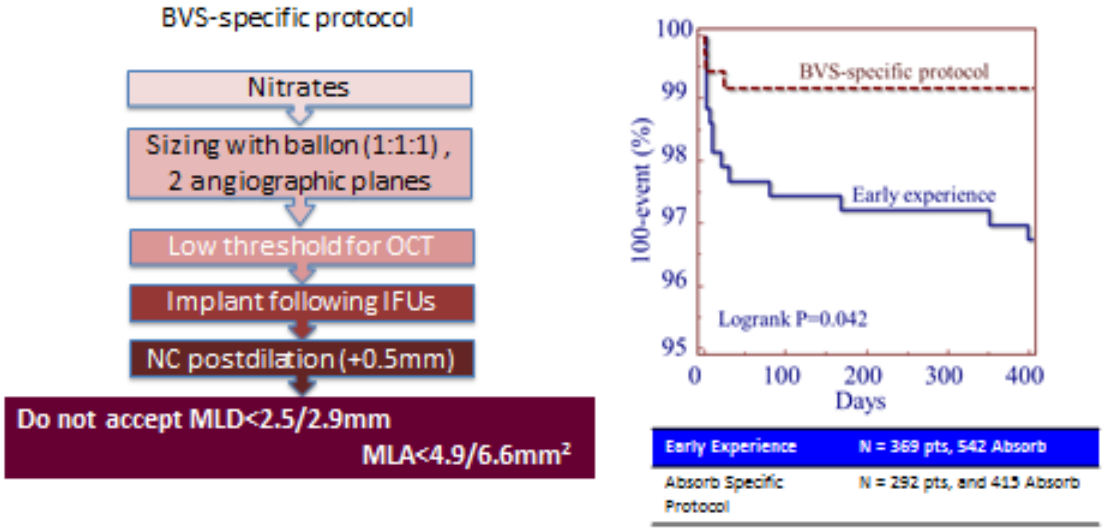


Figure 7.0-1 4Cities Registry 1 Year Scaffold Thrombosis Rates Out to 1 Year before and After Implementation of BVS Specific Treatment Protocol

Additionally, other real world trial and registry data since GHOST-EU has shown a reduction in 30 day and 1 year scaffold thrombosis rates (**Table 7.0-1**). Included in this table is the recent propensity matched analysis of Absorb subjects from GHOST EU to Xience subjects from the XIENCE V USA trial. The findings demonstrated that even with the earlier implant techniques used with Absorb, when accounting for multiple cofounders by propensity match analysis, the clinical outcomes between the two devices are similar [77]. These findings

from OUS registries and trials reinforce that the learning about optimal implantation technique is, like with prior new generation devices, an important factor in determining the clinical success of Absorb.

These findings are consistent with the results of ABSORB III in which showed that when implanted in appropriately sized vessels, Absorb had an excellent safety profile, even more comparable to Xience. Given the global learnings with Absorb, just like any other new technology, results are expected to improve as US physicians gain more experience.

Table 7.0-1 Stent Thrombosis in More Recent Real-World Registries

	30 Day Definite/Probable ST Rate	**1 Year Definite/Probable ST Rate**
REPARA [78]	0.9%	-
GABI-R [79]	1.0%	-
ABSORB First [80]	-	0.8%
GHOST EU Propensity [77]	-	1.8%
XIENCE V USA Propensity [77]	-	1.1%

8.0 Labeling, Physician Education, and Post Approval Commitments

Key Points:

- In a post-hoc RVD analysis, Absorb was associated higher event rates compared to Xience in very small vessels (QCA RVD < 2.25 mm).
- The Absorb label will include:
  - precaution language strongly recommending the use of quantitative imaging for vessels ≤ 2.75 mm
  - warning language to not implant Absorb if vessel size by quantitative imaging is < 2.5 mm
  - precaution language strongly recommending the use of high pressure post-diltation using non-compliant balloon
- Abbott Vascular will establish a comprehensive physician education program that consist of three main components that will consist of :
  - On-line modules on device basics and techniques

Abbott Vascular is committed to the responsible commercialization of Absorb. The commercialization plan will include:

- Precaution and warning specific to usage of Absorb in very small vessels
- Commitment to Physician Education
- Post-Approval Study

8.1 Precaution and Warning Language for Absorb Label

In the post-hoc RVD analysis, higher event rates were observed in both device arms when used in very small vessels (QCA RVD < 2.25 mm) but with a relatively greater increase in events for Absorb compared to Xience. A similar result was also seen in the diabetic sub-group. To address these observed differences in all subjects with vessels < 2.25 mm, including diabetics, the Absorb label will include the following precaution and warning language:

Precaution:

> In small vessels (visually assessed as ≤ 2.75 mm), on-line QCA or intravascular imaging is strongly recommended to accurately measure and confirm appropriate vessel sizing (≥ 2.5 mm).

Warning:

> If quantitative imaging determines a vessel size < 2.5 mm, do not implant Absorb. Implantation of the device in vessels < 2.5 mm may lead to an increased risk of adverse events such as myocardial infarction and scaffold thrombosis.

In addition to the learnings from ABSORB III, as noted in **Section 7.0**, international experience indicates that optimal clinical outcomes are achieved with Absorb on good lesion preparation, accurate scaffold sizing and liberal performance of high pressure post-dilatation. As such, the Absorb Label will also include a recommendation on post-dilatation as shown below:

Precaution:

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

This language will be reinforced in the physician education that is detailed in the next section.

8.2 Commitment to Physician Education

Even though Absorb represents first of its kind technology, the actual implant procedure is very similar to standard techniques for coronary stenting. The commercial experience outside the US has identified that given the structural differences of the Absorb scaffold compared to current generation DES, certain standard techniques need to be emphasized to optimize outcomes with Absorb.

These techniques include good lesion preparation to enhance delivery of the scaffold, appropriate vessel sizing to avoid very small vessels and respecting the expansion limit of the scaffold. Additionally, post-dilatation with a non-compliant balloon, sized 1:1 to the vessel using at least 16 atm of pressure, is strongly recommended to ensure full strut apposition and lesion expansion. This is consistent with advice from experienced Absorb users in commercially approved countries.

To ensure that all of these learnings are emphasized, Abbott Vascular will establish a robust and comprehensive physician education program. The physician education program will consistent of three main components. The first component is on-line modules inclusive of device basics, deployment techniques, and case reviews. The second component will include in-person education that includes live confirmation of device basics, review of deployment techniques, and interactive case discussions. The third component will be Abbott Vascular proctored cases. Each physician will be offered 3 to 5 monitored cases in which they will be instructed to use on-line QCA or intravascular imaging in cases with vessel ≤ 2.75 mm by visual assessment, to ensure Absorb is not used in vessels < 2.5 mm.

8.3 Post-Approval Study

Abbott Vascular is also committed to a robust post approval strategy, and has developed a post approval commitment plan. First, Abbott Vascular will continue to follow ABSORB III subjects through 5 years. Secondly, Abbott Vascular is also conducting ABSORB IV clinical trial which is designed to enroll 3000 randomized subjects, of which more than1000 have been currently enrolled. ABSORB III and ABSORB IV clinical trial subjects will be pooled for a total of 5000 subjects with 5 year follow-up, powered to demonstrate superiority of Absorb to Xience. Third, Abbott Vascular is collaborating with FDA to construct a post-approval registry that will include approximately 2000 - 3000 subjects at approximately 150 - 200 sites. The study design would evaluate low frequency events, effectiveness of labeling, education for very small vessels (< 2.5 mm), and confirm generalizability of the treatment with Absorb to real-world practice. The estimated follow-up of safety and effectiveness would be approximately 5 years.

9.0 Benefit / Risk Conclusion

Key Points:

- The ABSORB III trial met the primary endpoint, satisfying the FDA regulatory guidance for DES approval, and thus demonstrating a reasonable assurance of safety and effectiveness.
    - Absorb was non-inferior to standard of care Xience in the combined safety and effectiveness composite endpoint of TLF
- There were no statistical differences between Absorb and Xience for any of the individual endpoints of safety and effectiveness.
- Absorb preserves DES treatment effect and performs like a DES in the first year.
- Outcomes in appropriately sized vessels (≥ 2.25 mm) representing >80% of study population (over 1600 subjects) are highly similar between Absorb and Xience.
    - TLF difference between Absorb and Xience 1.2%
    - TV-MI difference between Absorb and Xience 0.6%
    - ST difference between Absorb and Xience 0.3%
- These results were achieved despite physicians having limited experience implanting the study device. Results are expected to further improve as physicians gain more experience.
- The ABSORB III trial, by showing comparable safety and effectiveness rates to Xience, demonstrates that the benefits of Absorb outweigh the risks.

The ABSORB III trial met the primary endpoint, satisfying the FDA regulatory guidance for DES approval. This included Absorb being non-inferior to standard of care, Xience in the combined safety and effectiveness composite endpoint of TLF at 1 year. There were no statistical differences between Absorb and Xience for any of the individual endpoints of safety and effectiveness. The outcomes of the ABSORB III trial demonstrate that Absorb preserves the effectiveness of DES over bare metal stent without leaving a permanent implant, and provides a reasonable assurance of safety and effectiveness. These results were achieved despite physicians having limited experience implanting the study device versus experience with thousands of Xience implants after 8 years of US approval. As is the case with other new technologies, results are expected to further improve as physicians gain more experience. This is supported by several trials and registries which identified that the continued use of optimal Absorb techniques has contributed to improved outcomes [13-16]. Most importantly, when implanted in appropriately sized vessels, Absorb had an even better safety profile, with lower and almost identical event rates to Xience. In the RVD $\geq$ 2.25 mm subgroup, the two devices only had observed differences in TLF of 1.2%, TV-MI of 0.6%, and device thrombosis of 0.3%, all clinically similar between the two devices. These findings reinforce that when Absorb is placed in appropriately sized vessels, the benefits of Absorb at 1 year are comparable to that of Xience.

The observed 1 year cardiac death rates for Absorb were higher compared to Xience. However, historical data demonstrated that the performance of Xience as it pertains to cardiac death was unusually low in the ABSORB III trial. Compared to other DES trials, Absorb shows comparable cardiac death rates.

Specific to the effectiveness endpoints, Absorb showed very low and similar ID-TLR rates compared to Xience (3.0% and 2.5%, respectively), preserving the expected effectiveness of DES over bare metal stents. Additionally, the powered secondary efficacy endpoints of angina, ID-TVR, and all revascularization were very comparable between the two devices, reinforcing the effectiveness of Absorb.

Long-term data from ABSORB Cohort B, ABSORB EXTEND, and ABSORB II provided evidence that between 1 and 2 years the increase in event rates for Absorb is similar to that of historical Xience trials. Additionally, out to 3 and 5 years the rates of TLF and MACE for Absorb show an emerging trend for reduction as compared to Xience, consistent with what is expected given full resorption by 36 months. These long-term observations are to be further confirmed in the ABSORB IV trial but not required for initial regulatory approval.

In summary, the ABSORB III trial, by showing comparable safety and effectiveness rates to Xience, satisfies the regulatory requirements for DES approval and demonstrates that the benefits of Absorb outweigh the risks. This is further reinforced by data which show that when Absorb is placed in appropriately sized vessels its safety profile is improved compared to Xience. Absorb offers a new PCI therapeutic option for patients that do not want a permanent implant with the assurance of being as safe and effective as a DES within the first year.

10.0 Supporting Appendices and List of References

Appendix 1: Supplementary Information for ABSORB III Trial

Appendix 2: Enrollment in Primary Analysis Group by Site

Appendix 3: ABSORB III Lead-In Group

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