Draft Panel Questions (8 Questions)
Absorb GT1™ Bioresorbable Vascular Scaffold (BVS) System

Evaluation of Safety and Effectiveness

The principal safety and effectiveness information for the Absorb GT1 Bioresorbable Vascular Scaffold (BVS) System is derived from the ABSORB III randomized trial, in which 2,008 subjects were randomized 2:1 to either the BVS (n=1,322 subjects) or the XIENCE stent (n=686 subjects). The sponsor proposed the following Indications for Use for the BVS:

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

The primary endpoint for the ABSORB III trial was target lesion failure (TLF) rate at 12 months. TLF is a composite of safety events (cardiac death and target vessel MI) and effectiveness events (ischemia-driven target lesion revascularization). The ABSORB III TLF results are shown in Table 1A.

Table 1A. ABSORB III Primary Endpoint Analysis (Primary Analysis Group, ITT Population, Per-Protocol MI Definition)

	BVS (N=1322)	XIENCE (N=686)	Difference (95% CI[1])	Non-Inferiority P-Value[2]
1-Year TLF Rate	7.8% (102/1313)	6.1% (41/677)	1.71% (-0.51%, 3.93%)	0.0070

[1] 95% confidence interval by Farrington-Manning method.
[2] One-sided p-value by using Farrington-Manning non-inferiority test statistic with non-inferiority margin of 4.5%, to be compared with a one-sided significance level of 0.025.
Note: N = the total number of subjects. TLF = Target Lesion Failure

The absolute difference of the TLF rate between treatment groups was 1.71% in favor of the XIENCE group. The corresponding 95% confidence interval was (-0.51%, 3.93%), the upper bound of which was less than the pre-specified non-inferiority margin of 4.5%; therefore, statistical non-inferiority was achieved.

The rates of the individual components of the TLF composite endpoint are shown in Table 1B. The rates of cardiac death, target vessel MI, and ID-TLR numerically favored the XIENCE group.

Table 1B. Rates of the Components of the TLF Composite

	BVS (N=1322)	XIENCE (N=686)	Difference [95% CI][1]
TLF Safety Components			
Cardiac Death	0.6% (8/1313)	0.1% (1/677)	0.46% [-0.29%, 1.06%]
Target Vessel MI	6.0% (79/1313)	4.6% (31/677)	1.44% [-0.74, 3.39%]
TLF Effectiveness Component			
ID-TLR	3.0% (40/1313)	2.5% (17/677)	0.54% [-1.14%, 1.96%]

[1] Without multiplicity adjustment.
Note: ID-TLR = ischemia-driven target revascularization

Stent/scaffold thrombosis is an important mechanism for cardiac death or target vessel MI. The rate of ARC definite plus probable scaffold/stent thrombosis was more than 2-fold higher in the BVS group vs. the XIENCE group. (Table 1C).

Table 1 C. Cumulative ARC Definite + Probable Scaffold/Stent Thrombosis Rate through 393 Days

	BVS (N=1322)	XIENCE (N=686)	Difference [95% CI][1]
Definite	1.38% (18/1301)	0.74% (5/675)	0.64 [-0.46, 1.54%]
Definite + Probable	1.54% (20/1301)	0.74% (5/675)	0.80 [-0.32, 1.72%]

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

Panel Question 1: Safety and Effectiveness

Q1: In the ABSORB III trial, the BVS met the criterion for non-inferiority to XIENCE for the 1-year TLF primary endpoint. However, the rates of the individual components of TLF (most notably target vessel MI) and definite plus probable stent thrombosis were numerically higher in the BVS group vs. the XIENCE group. Please comment on whether the ABSORB III results provide adequate evidence of clinical non-inferiority of the BVS as compared to the XIENCE stent with regard to (A) safety and (B) effectiveness in the patient population described by the proposed indications for use.

Small Vessel Subgroup Analysis

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

In the ABSORB III trial, the angiographic core lab found that 19% of ITT subjects (18% and 20% of BVS and XIENCE subjects, respectively) underwent treatment of an artery with a QCA-assessed RVD of <2.25 mm.

Table 2A shows a post-hoc analysis of the rates of 1-year TLF, the components of TLF, and ARC definite plus probable scaffold/stent thrombosis for the BVS and XIENCE groups, stratified by angiographic core lab-assessed RVD ≥2.25 mm or <2.25 mm.

Table 2A. 1-Year Clinical Outcomes Stratified by Core Laboratory Assessed RVD – Per-Subject Analysis (Primary Analysis Group, ITT, Per Protocol MI Definition)

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

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

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

Table 2B shows an additional post-hoc analysis of the 1-year TLF rates, the components of TLF, and definite plus probable scaffold/stent thrombosis for the BVS vs. XIENCE groups in subjects with diabetes mellitus, stratified by a QCA-assessed RVD ≥2.25 mm or <2.25 mm.

Table 2B. 1-Year Clinical Outcomes in Diabetic Mellitus Subjects Stratified by RVD – Per-Subject Analysis (Primary Analysis Group, ITT Population, Per Protocol MI Definition)

	All DM			DM with RVD ≥2.25 mm			DM with RVD <2.25 mm		
	BVS N=416	XIENCE N=224	Dif [95%CI][1]	BVS N=325	XIENCE N=177	Dif [95%CI][1]	BVS N=88	XIENCE N=45	Dif [95%CI][1]
TLF	10.7%	9.1%	1.61% [-3.63%, 6.21%]	7.2%	7.5%	-0.31% [-5.73%, 4.23%]	23.9%	15.6%	8.31% [-6.99%, 20.90%]
CD	0.5%	0.0%	0.49% [-1.27%, 1.76%]	0.3%	0.0%	0.31% [-1.86%, 1.74%]	1.1%	0.0%	1.14% [-6.78%, 6.16%]
TV-MI	9.0%	7.3%	1.73% [-3.12%, 5.92%]	6.2%	6.9%	-0.67% [-5.90%, 3.66%]	19.3%	8.9%	10.43% [-3.27%, 21.31%]
ID-TLR	5.6%	3.6%	1.96% [-1.88%, 5.16%]	3.4%	1.1%	2.28% [-1.03%, 5.01%]	13.6%	13.3%	0.30% [-13.73%, 11.52%]
Scaff/stent Thromb	3.2%	1.4%	1.84% [-1.06%, 4.22%]	1.3%	0.6%	0.68% [-2.05%, 2.67%]	10.6%	4.4%	6.14% [-5.34%, 15.07%]

[1] Without multiplicity adjustment.

Note: CD = cardiac death; DM = diabetes mellitus; ID-TLR = ischemia-driven target revascularization; N = the total number of subjects; RVD = reference vessel diameter; Scaff/stent Thromb = ARC definite + probable stent thrombosis; TV-MI = target vessel MI

The event rate *differences* between the BVS group and the XIENCE group were more pronounced in subjects with diabetes mellitus and a QCA-assessed <2.25 mm RVD treated artery (again most notably for the rates of TLF, target vessel MI, and stent thrombosis) compared with diabetic subjects with a ≥2.25 mm RVD.

Panel Questions 2 to 4: BVS Use in Small Coronary Arteries

Q2: Please comment on the clinical significance of the higher event rates observed when a BVS was implanted in an artery with a QCA-assessed RVD of <2.25 mm.

Q3: The sponsor proposed the following precaution and warning for the Absorb GT1 BVS Instructions For Use:

> *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.*

a. Please comment on the adequacy of the proposed Precaution to recommend that operators utilize on-line QCA or intravascular imaging to confirm that the target vessel is appropriately sized for safe and effective use of a BVS. In your discussion, please consider whether the BVS clinical data and operator expertise adequately support the proposed visually-assessed ≤2.75 mm diameter threshold for the use of quantitative imaging to confirm the selection of appropriately sized vessels for scaffold implantation.

b. Please comment on the adequacy of the proposed Warning against the use of a BVS in <2.5 mm vessels.

Q4: Please comment on whether or not the Instructions For Use should include additional language regarding an increased risk for adverse events when a BVS is implanted in very small vessels (angiographic core lab-assessed RVD < 2.25 mm) in patients with diabetes mellitus.

Duration of Follow-Up

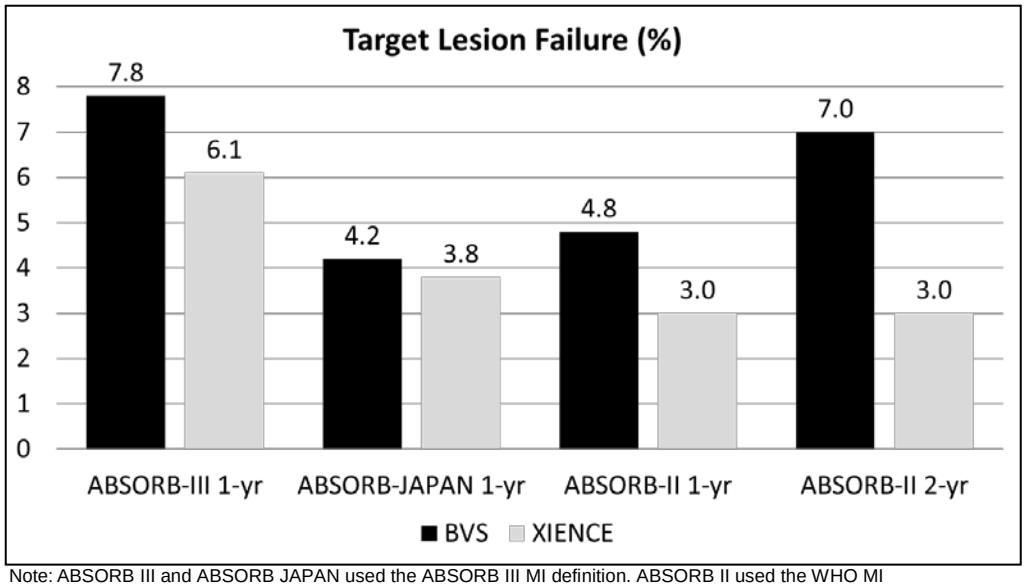
The BVS is designed to provide adequate mechanical support through 6 months post-deployment. It is estimated that the process of complete BVS resorption requires 24 to 36 months, and some potential advantages of a bioresorbable coronary scaffold may be not be realized until bioabsoption is far advanced or complete.

In the ABSORB III pivotal study, the BVS met its non-inferiority endpoint for the rate of TLF at 12 months but with the caveats as presented in Question 1. There are additional clinical and imaging outcomes data for BVS patients from other non-US studies to supplement the ABSORB III results (see Appendix 3 – Appendix 7). Table 5 shows the number of BVS subjects and follow-up duration for the ABSORB BVS Program reviewed in this PMA.

Table 5: BVS Subject Follow-up

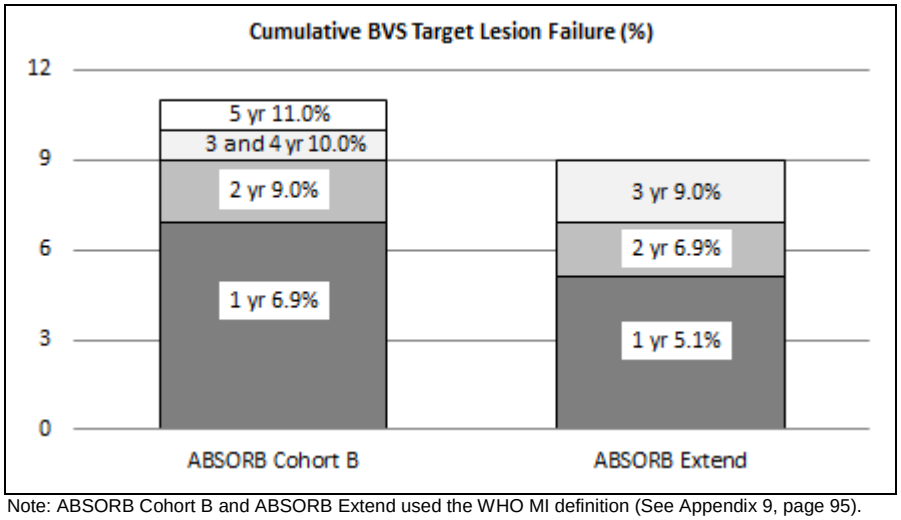
	1 year	2 years	3 years	4 years	5 years
ABSORB Cohort B	101	100	100	100	100
ABSORB EXTEND	811	807	613		
ABSORB II	331	328			
ABSORB Japan	265				
ABSORB III	1313				
Total	**2821**	**1235**	**713**	**100**	**100**

Figure 1 and Figure 2 show the TLF rates from the last available follow-up from the randomized trials (ABSORB III, ABSORB Japan, and ABSORB II) and single arm studies (ABSORB Cohort B and ABSORB Extend), respectively.



Note: ABSORB III and ABSORB JAPAN used the ABSORB III MI definition. ABSORB II used the WHO MI definition (See Appendix 9, page 93 and page 95).

Figure 1: Target lesion failure rates from the last available follow-up of the BVS randomized trials



Note: ABSORB Cohort B and ABSORB Extend used the WHO MI definition (See Appendix 9, page 95).

Figure 2: Target lesion failure rates from the last available follow-up of the BVS single arm studies

Panel Question 5: Duration of Follow-Up

Q5: Please comment on whether or not the PMA includes adequate follow-up data in a sufficient portion of the patient population identified in the proposed indications to support safety and effectiveness. If the duration of follow-up is insufficient, please comment on how much additional follow-up data from the ABSORB III trial should be provided to demonstrate a reasonable assurance of BVS safety and effectiveness.

BVS Post-Dilatation

In the ABSORB III trial, pre-dilatation of the target lesion was required prior to BVS implantation. In contrast, post-dilatation was left up to the discretion of the operator. If post-dilatation was performed, it was recommended that the BVS should not be dilated beyond 0.5 mm above the nominal diameter so as to avoid scaffold damage.

In the ABSORB III BVS group, post-dilatation was performed in 898 of 1,385 (64.8%) lesions and 765 of 1,219 (62.8%) subjects, and not performed in 487 of 1,385 (35.2%) lesions and 545 of 1,219 (37.2%) subjects. The rate of BVS implantation procedural success was slightly lower when post-dilatation was performed; and post-dilatation was not associated with a consistent improvement in the 1-year rates of TLF, cardiac death, target vessel MI, ischemia-driven TLF, and scaffold thrombosis (Table 6A).

Table 6A. Comparison of Procedural Success and Event Rates between Post-Dilatation with Non-Compliant vs. Not Post-dilatation in the BVS Group

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

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

In the comparison of procedural success and event rates between post-dilatation with a non-compliant balloon vs. no post-dilatation, the data must be interpreted with caution because subjects were not randomized to post-dilatation versus no post-dilatation.

The BVS Instructions For Use includes the following statement in the Precautions section:

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

Panel Question 6: Post-dilatation

Q6: Please discuss the adequacy of the ABSORB III trial data to support a strong recommendation that post-dilatation should be performed when implanting a BVS.

Post-Approval Study

The Sponsor provided the following post-approval commitments:

- Continue ABSORB III follow-up through 5 years
- Continue ABSORB IV

    - Enrolling up to 3,000 patients
    - Pooled with ABSORB III for superiority to XIENCE at 5 years
- Conduct a post-approval study
    - 2,000 – 3,000 patients
    - Approximately 150 – 200 sites
    - Broader patient population and physicians
    - Analyze low frequency events and confirm generalizability to real-world practice
    - Imaging sub-group to evaluate effectiveness of labeling and training for small vessel (<2.5 mm) enrollment
    - 5 year follow-up of safety and effectiveness outcomes

Panel Question 7: Post-Approval Study

Q7: Please comment on whether the sponsor's proposed post-approval commitments are appropriate and whether additional elements or objectives should be considered.

Labeling

Draft labeling was provided by the sponsor in the Panel Pack.

Panel Question 8: Labeling

Q8. Please comment on the proposed contraindications, warnings, and precautions in the labeling.