September 21, 2016

Medical Device Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Bio-absorbable coronary stent
Brand Name	Absorb GT1 Bioresorbable Vascular Scaffold System
Applicant	Abbott Vascular Japan Co., Ltd.
Date of Application	April 30, 2015 (Application for marketing approval)

Results of Deliberation

In the meeting held on September 21, 2016, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and concluded that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product should be designated as a medical device subject to a use-results survey and approved with the following conditions. The product is classified as a specially controlled medical device and not classified as a specially designated maintenance-and-management-required medical device. The product is not classified as a biological product or a specified biological product.

The duration of the use-results survey should be 7 years.

Conditions of Approval of the Marketing Application

1. The applicant is required to take necessary measures in cooperation with related academic societies. For instance, guidance for proper use of the product and skills training should be provided to surgeons to ensure that they fully understand the efficacy and safety of the product and have established knowledge and experience in relevant procedures.
2. The applicant is required to conduct a use-results survey involving all patients treated with the product in the post-marketing period until data from a certain number of patients have been gathered, to submit annual reports on the results of analyses of long-term outcomes to the Pharmaceuticals and Medical Devices Agency (PMDA), and to take appropriate measures as necessary.
3. The applicant is required to work with related academic societies to collect information on the occurrence of stent thrombosis for a certain period of time after approval and to take appropriate measures as necessary.
4. The applicant is required to submit, to PMDA, annual reports on the results of analyses of long-term outcome data from patients who participated in the submitted clinical studies and to take appropriate measures as necessary.

Review Report

September 5, 2016
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Bio-absorbable coronary stent (to be newly created)
Brand Name	Absorb GT1 Bioresorbable Vascular Scaffold System
Applicant	Abbott Vascular Japan Co., Ltd.
Date of Application	April 30, 2015
Reviewing Office	Office of Medical Devices III

Review Results

September 5, 2016

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Bio-absorbable coronary stent (to be newly created)
Brand Name	Absorb GT1 Bioresorbable Vascular Scaffold System
Applicant	Abbott Vascular Japan Co., Ltd.
Date of Application	April 30, 2015

Results of Review

Absorb GT1 Bioresorbable Vascular Scaffold System (hereinafter referred to as "Absorb GT1 BVS") consists of a scaffold and a delivery system that is a rapid exchange balloon catheter. The scaffold made from bioresorbable poly(L-lactide) is crimped to the balloon at the tip of the delivery system. The scaffold is coated with a drug-polymer layer containing bioresorbable poly(D, L-lactide), and a cytostatic drug (everolimus).

The applicant submitted the non-clinical data supporting the physiochemical properties, biological and mechanical safety, stability and durability, performance of Absorb GT1 BVS, and data on study results supporting the method of use of the product. No particular problems were observed in the non-clinical aspects.

The applicant submitted clinical evaluation data on Absorb GT1 BVS from a Japanese clinical study with the former model AVJ-301 (Study AVJ-301, a multicenter, prospective, randomized, controlled study [266 patients in the AVJ-301 group and 134 patients in the XIENCE group]), a clinical study in the United State (the ABSORB III study, a multicenter, prospective, randomized, controlled study [1322 patients in the AVJ-301 group and 686 patients in the XIENCE group]), and a pharmacokinetic (PK) study. Data from the ABSORB Cohort A study, ABSORB Cohort B study, the ABSORB EXTEND study, the ABSORB II study, and the ABSORB China study were also submitted as reference data.

The primary endpoint of Study AVJ-301 was the incidence of target lesion failure (TLF) at 12 months (393 days). The incidence of TLF was 4.2% in the AVJ-301 group and 3.8% in the XIENCE group, demonstrating the non-inferiority of AVJ-301 to XIENCE. In the ABSORB III study, the TLF rate (incidence of TLF) at 12 months (393 days), the primary endpoint, was 7.8% in the AVJ-301 group and 6.1% in the XIENCE group, demonstrating the non-inferiority of AVJ-301 to XIENCE. AVJ-301, however, tended to be associated with a high incidence of stent thrombosis (ST) or myocardial infarction (MI). The causes of ST were investigated. The struts of AVJ-301 are characteristically thicker than those of conventional metal stents. In Study AVJ-301 and the ABSORB III study, the incidence of ST tended to be high in subjects with a small vessel size or a small post-procedure minimal lumen diameter. To prevent the occurrence of ST, appropriate measurement of the reference vessel diameter (RVD), selection of a suitable stent size, and adequate post-dilatation were considered essential. MI cases are classified into perioperative MI or spontaneous MI caused by ST. Perioperative MI rarely raises a clinical concern. The aforementioned measures should be taken to prevent ST from occurring.

The long-term outcomes of treatment with Absorb GT1 BVS at ≥1 year post-implantation in Study AVJ-301 showed a higher incidence of TLF at ≥1 year in the AVJ-301 group than in the XIENCE group. Approximately half the TLF cases in the AVJ-301 group were events related to very late stent thrombosis (VLST) that occurred at ≥1 year. The possible primary causes of VLST were inadequate dilatation, mal-apposition, and under-sized stents. Since improved procedures (appropriate RVD measurement, suitable stent size selection, and adequate post-dilatation) are expected to reduce the risk of VLST, VLST events reported in the clinical studies are considered clinically tolerable.

However, given that no sufficient evidence has been accumulated on the causes of ST or VLST associated with novel Absorb GT1 BVS and that ST and VLST may result in serious adverse events, including MI, it is necessary to verify the effectiveness of the aforementioned risk reduction measures in reducing the incidence of ST and VLST in the post-marketing setting in Japan. A use-results survey, therefore, should be conducted in all patients treated with Absorb GT1 BVS in the post-marketing setting to periodically analyze long-term outcomes of treatment with Absorb GT1 BVS, including the occurrence of ST and VLST, and appropriate measures should be taken as necessary. In addition, for safe introduction of Absorb GT1 BVS into Japan, the applicant should expand the distribution of Absorb GT1 BVS in a stepwise manner while periodically analyzing long-term outcomes of treatment with Absorb GT1 BVS.

As a result of its review, PMDA has concluded that Absorb GT1 BVS may be approved for the following intended use with the conditions shown below, and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

Treatment of patients with symptomatic ischemic heart disease due to *de novo* coronary artery lesions (length ≤24 mm) with a reference vessel diameter of ≥2.5 mm and ≤3.75 mm

Conditions of Approval

1. The applicant is required to take necessary measures in cooperation with related academic societies. For instance, guidance for proper use and skills training should be provided to surgeons to ensure that they fully understand the efficacy and safety of the product and have established knowledge and experience in relevant procedures.
2. The applicant is required to conduct a use-results survey involving all patients treated with the product in the post-marketing period until data from a certain number of patients have been gathered, to submit annual reports on the results of analyses of long-term outcomes to the Pharmaceuticals and Medical Devices Agency (PMDA), and to take appropriate measures as necessary.
3. The applicant is required to work with related academic societies to collect information the occurrence of stent thrombosis for a certain period of time after approval and to take appropriate measures as necessary.
4. The applicant is required to submit, to PMDA, annual reports on the results of analyses of long-term outcome data from patients who participated in the submitted clinical studies and to take appropriate measures as necessary.

Review Report

September 5, 2016

I. Product Submitted for Approval

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Bio-absorbable coronary stent (to be newly created)
Brand Name	Absorb GT1 Bioresorbable Vascular Scaffold System
Applicant	Abbott Vascular Japan Co., Ltd.
Date of Application	April 30, 2015
Proposed Intended Use	Treatment of patients with ischemic heart disease due to *de novo* coronary artery lesions (length ≤24 mm) with a reference vessel diameter of ≥2.5 mm and ≤3.75 mm

II. Product Overview

Absorb GT1 Bioresorbable Vascular Scaffold System ("Absorb GT1 BVS") consists of a scaffold and a delivery system that is a rapid exchange balloon catheter. Absorb GT1 BVS is supplied with the scaffold crimped to the balloon at the distal end of the delivery system (Figure 1). The scaffold is made from bioresorbable poly(L-lactide) (PLLA) so that the scaffold degrades and resorbs after it physically maintains the vessel lumen patency for a period necessary for revascularization. The scaffold is coated with a cytostatic drug everolimus and a bioresorbable polymer poly(D,L-lactide) (PDLLA) to inhibit neointimal growth after implantation. Table 1 presents the size range of Absorb GT1 BVS available.

Figure 1. Product photographs (left, the scaffold; right, the scaffold crimped to the delivery system)

Table 1. Scaffold size range

Design	Nominal diameter (mm)	Nominal length (mm)				
		8	12	18	23	28
Small	2.5	○	○	○	○	○
	3.0	○	○	○	○	○
Medium	3.5	-	○	○	○	○

Everolimus used in the scaffold of Absorb GT1 BVS is supplied by Novartis Pharma AG and its drug substance is identical to that used to manufacture Certican Tablets 0.25 mg, 0.5 mg, and 0.75 mg

(Approval Nos. 21900AMX00043000, 21900AMX00044000, and 21900AMX00045000, respectively; Novartis Pharma K.K.). Everolimus is also used in Abbott's XIENCE drug-eluting stent series, including the XIENCE V drug-eluting stent (Approval No. 22200BZX00076000) (hereinafter referred to as "XIENCE V"). The dose of the drug per unit area used in the Absorb GT1 BVS is the same as that used in the XIENCE drug-eluting stent series, but Absorb GT1 BVS contains a higher total amount of everolimus than the XIENCE series. The coating of the stent also differs between these products; the XIENCE drug-eluting stents are coated with a non-bioresorbable polymer, whereas the stent of Absorb GT1 BVS uses a bioresorbable polymer as a coating material.

III. Summary of the Data Submitted and the Outline of Review Conducted by the Pharmaceuticals and Medical Devices Agency

The data submitted by the applicant in support of the present application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors for the Expert Discussion on the product declared that it does not fall under Item 5 of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/20 dated December 25, 2008).

1. History of development, use in foreign countries, and other information

1.A. Summary of the submitted data

1.A.(1) History of development

Conventionally, coronary artery stenotic lesions in patients with ischemic heart disease were primarily treated by drug therapy or percutaneous transluminal coronary angioplasty (PTCA). Bare-metal stents (BMS) were developed later. BMS physically maintains the vessel lumen patency, thereby enabling prevention of acute vessel recoil and remodeling. In addition, drug-eluting metal stents coated with a cytostatic drug (drug-eluting stent [DES]) allowed local inhibition of neointimal proliferation, which has resulted in a marked reduction in the incidence of restenosis. Cypher Stent (Approval No. 21600BZY00136000, Johnson & Johnson K.K.) using sirolimus as a cytostatic drug is the first DES that was introduced into Japan in 2004. In 2010, XIENCE V with everolimus (Abbott Vascular Japan Co., Ltd.) was marketed in Japan. Subsequently, the following stents that use the same drug and coating layer as those of XIENCE V, but have a different stent design or delivery system were also introduced into Japan: XIENCE PRIME Drug-Eluting Stent (Approval No. 22400BZX00145000) (XIENCE PRIME), XIENCE PRIME SV Drug-Eluting Stent (Approval No. 22500BZX00070000), XIENCE Xpedition Drug-Eluting Stent (Approval No. 22500BZX00309000) (XIENCE Xpedition), and XIENCE Alpine Drug-Eluting Stent (Approval No. 22600BZX00529000). This XIENCE series is collectively called "XIENCE stent."

According to the literature based on therapeutic experience with PTCA, the patency of a stenosed blood vessel needs to be maintained for 3 to 6 months to prevent vessel recoil and remodeling after dilatation at the stenosed blood vessel.[1,2,3] On the other hand, conventional metal stents (BMSs and DESs) which prevent vessel recoil and remodeling remain in the body permanently. Abbott Vascular (US) developed bioresorbable vascular scaffold (BVS), which physically maintains the vessel lumen patency for a period necessary for revascularization and eventually degrades and resorbs so that the scaffold does not remain

in the blood vessel. The disappearance of the scaffold from the body is expected to enable the blood vessel to restore the mobility and recover from positive remodeling in the late postoperative phase, as well as to reduce late inflammatory reaction and thrombosis, and allow low invasive examinations by computed tomography (CT).

Poly lactic acid (PLA) is a bioresorbable material that has already been used in approved medical devices, including orthopedic screw Super Fixsorb 30 (Approval No. 21500BZZ00473000, Takiron Inc.), which is made of PLLA, and bioresorbable suture Vicryl (Approval No. 15700BZY01341000, Johnson & Johnson K.K.). Whereas PDLLA is used as a drug carrier in approved DESs, no bioresorbable scaffold products have been approved in Japan to date.

The Absorb GT1 BVS scaffold provides transient arterial mechanical support and eventually degrades through hydrolysis, resulting in full resorption, except for the scaffold marker (platinum). An animal study in pigs treated with BVS-B, a previous generation of Absorb GT1 BVS, demonstrated that BVS-B had been degraded and resorbed at approximately 36 months post-implantation. Optical coherence tomography (OCT) at 5 years after scaffold implantation in the human coronary artery showed that the struts of BVS-B resorbed in the body and did not remain in the body (Figure 2).

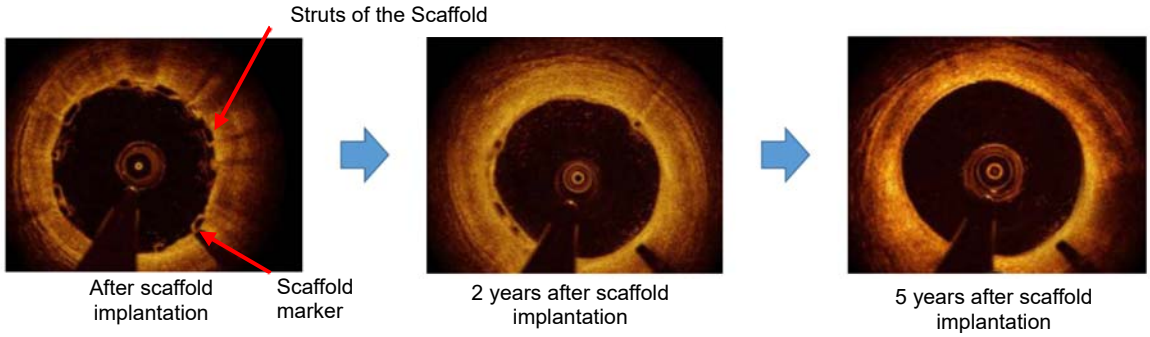


Figure 2. Change over time after BVS-B implantation (OCT images)

In the course of development of Absorb GT1 BVS, various changes were made to the Absorb products to add more sizes, increase productivity, and improve device performance. Table 2 presents the history of changes to the Absorb GT1 BVS. BVS-A, AVJ-301, and Absorb GT1 BVS are collectively called "BVS."

Table 2. Changes made during the product development process

Model	Change from previous generation
BVS-A*	-
BVS-B	• Scaffold design
AVJ-301**	• Scaffold design • Size range (added sizes)
Absorb GT1 BVS	• Delivery system (the same scaffold as that of AVJ-301)

* Initial model

** Model used in the Japanese clinical study (Study AVJ-301) and the US clinical study (ABSORB III study)

1.A.(2) Use in foreign countries

Tables 3 and 4 present the situation of certification/approval and sales of Absorb GT1 BVS and AVJ-301 in foreign countries.

Table 3. Use in major foreign countries (Absorb GT1 BVS) (August 2016)

Country/ region	Brand name	Date of certification/authorization	Intended use or indication	Sales performance*
US	Absorb GT1 Bioresorbable Vascular Scaffold System	July 5, 2016 (P150023)	Treatment of patients with ischemic heart disease due to *de novo* coronary artery lesions (length ≤24 mm) with a reference vessel diameter of ≥2.5 to ≤3.75 mm	-
EU		April 30, 2015	Treatment of patients with ischemic heart disease due to *de novo* coronary artery lesions (length less than the nominal length) with a reference vessel diameter of ≥2.0 to ≤3.8 mm**	[redacted]
Others	-	-	-	[redacted]
			Total	[redacted]

* Survey period, May 2015 to June 2016

** [redacted]

Table 4. Use in major foreign countries (AVJ-301) (August 2016)

Country/ region	Brand name	Date of certification/authorization	Intended use or indication	Sales performance*
EU	ABSORB Bioresorbable Vascular Scaffold System	August 13, 2012	Treatment of patients with ischemic heart disease due to *de novo* coronary artery lesions (length less than the nominal length) with a reference vessel diameter of ≥2.0** to ≤3.8 mm	[redacted]
Australia		March 9, 2013	Treatment of patients with ischemic heart disease due to *de novo* coronary artery lesions (length less than the nominal length) with a reference vessel diameter of ≥2.0** to ≤3.8 mm	[redacted]
Others	-	-	-	[redacted]
			Total	[redacted]

* Survey period, August 2012 to June 2016

** [redacted]

1.A.(3) Occurrence of malfunctions

Tables 5 to 8 present the incidence of major malfunctions and adverse events (those with an incidence of ≥0.01%) related to Absorb GT1 BVS and AVJ-301 in foreign countries.

Table 5. Incidence of malfunctions in foreign countries (Absorb GT1 BVS)

Type of malfunction	Number of malfunctions	Incidence (%)
Improper use of device*	[redacted]	0.0181%
Difficulty in removal		0.0181%
Difficulty in placement		0.0109%
Device not reaching lesion (not passing through a lesion)		0.0109%
No information evidencing malfunction**		0.1158%

* The product not used in accordance with the method of use or precautions specified in the Instructions for Use caused decreased device performance or damage to the device.

** No device malfunction was observed, but adverse health effects were reported.

Table 6. Incidence of malfunctions in foreign countries (AVJ-301)

Type of malfunction	Number of malfunctions	Incidence (%)
Difficulty in removal	[redacted]	0.0926%
Improper use of device*	[redacted]	0.0767%
Inadequate balloon dilatation	[redacted]	0.0677%
Difficulty in placement	[redacted]	0.0651%
Device rupture	[redacted]	0.0640%
Balloon rupture	[redacted]	0.0445%
Device not reaching lesion (not passing through a lesion)	[redacted]	0.0439%
Device breakage	[redacted]	0.0249%
Difficulty in positioning**	[redacted]	0.0238%
Leakage from system	[redacted]	0.0206%
Placement failure	[redacted]	0.0132%
Stent deformity/damage	[redacted]	0.0132%
Device kink	[redacted]	0.0122%
No information evidencing malfunction***	[redacted]	0.3250%

* The product not used in accordance with the method of use or precautions specified in the Instructions for Use caused decreased device performance or damage to the device.

** This device came into contact with another device (e.g., a post-dilatation balloon or intravascular diagnostic imaging system not re-passing or being difficult to re-pass, or not passing through the placed scaffold or stent).

*** No device malfunction was observed, but adverse health effects were reported.

Table 7. Incidence of adverse events in foreign countries (Absorb GT1 BVS)

Adverse event	Number of adverse events	Incidence (%)
Additional intervention (non-surgical)	[redacted]	0.0941%
Thrombosis	[redacted]	0.0941%
Hospitalization/prolonged hospitalization	[redacted]	0.0615%
Myocardial infarction	[redacted]	0.0398%
Angina pectoris	[redacted]	0.0326%
Drug therapy	[redacted]	0.0290%
Death	[redacted]	0.0109%
Cardiogenic shock	[redacted]	0.0109%
Increased enzyme	[redacted]	0.0109%
Intimal dissection	[redacted]	0.0109%

Table 8. Incidence of adverse events in foreign countries (AVJ-301)

Adverse event	Number of adverse events	Incidence (%)
Additional intervention (non-surgical)	[redacted]	0.2768%
Thrombosis	[redacted]	0.2075%
Hospitalization/prolonged hospitalization	[redacted]	0.1916%
Angina pectoris	[redacted]	0.1170%
Myocardial infarction	[redacted]	0.1043%
Stenosis	[redacted]	0.0810%
Drug therapy	[redacted]	0.0783%
Intimal dissection	[redacted]	0.0677%
Death	[redacted]	0.0418%
Electrocardiographic change	[redacted]	0.0275%
Increased enzyme	[redacted]	0.0175%
Cardiac arrest	[redacted]	0.0175%
Perforation	[redacted]	0.0175%
Aneurysm	[redacted]	0.0148%
Ischaemia	[redacted]	0.0143%
Obstruction	[redacted]	0.0143%
Delayed intervention due to device malfunction	[redacted]	0.0127%
No health injury (effect)*	[redacted]	0.1614%

* A product malfunction was reported with no adverse health effect identified.

2. Data relating to design and development

2.(1) Performance and safety specifications

2.(1).A. Summary of the submitted data

The performance and safety specifications defined for Absorb GT1 BVS include the following: scaffold percent recoil; uniformity of scaffold expansion; percent change in scaffold length from pre- to post-expansion; scaffold radial strength (radial force); scaffold expansion diameter limit, scaffold durability (accelerated fatigue); drug identity; total drug content; drug content uniformity; drug release; the amounts of residual solvents, impurities, and degradation products; scaffold coating integrity; scaffold's number-average molecular weight (M_n); magnetic resonance imaging (MRI) compatibility; scaffold movement; pullback into guiding catheter; nominal pressure; catheter preparation; balloon deflation time; maximum inflation pressure; tensile strength; catheter shaft pressure resistance; inner member collapse; balloon fatigue; particulate matter; hydrophilic coating; radiopacity; maximum guide wire diameter; radial strength (radial force) at [redacted]; biological safety; sterility assurance; and bacterial endotoxins.

2.(1).B. Outline of the review conducted by PMDA

Absorb GT1 BVS is intended to maintain the vessel lumen patency for a certain period of time and then disappear after it serves its purpose. PMDA asked the applicant to provide the justification of the specification limits for the following parameters:

1) Specification limits for M_n of the scaffold
2) Specification limits for pulsatile fatigue test

The applicant's response:

1) The lower limit of M_n of the scaffold (initial molecular weight) was calculated according to its design requirements based on the molecular weight at the time when the radial strength of the scaffold started declining in the *in vitro* degradation test of the scaffold.

    - Relationship between radial strength and M_n
      As shown in Figure 3, no correlation was observed between the radial strength and M_n measured in the *in vitro* degradation test until M_n decreased to [redacted] Da.

Figure 3. Relationship between radial strength and M_n

- Calculation of the initial molecular weight (lower limit of M_n of the scaffold defined in the specifications)
  The exponential decay equation of molecular weights is supported by the literature[4,5,6] and the results of the *in vitro* and *in vivo* degradation tests (Figure 4). The slope is determined by initial molecular weight $M_n(0)$ and rate constant k, and k depends on [redacted] but not on [redacted]. Considering the design concept "Maintenance of the radial strength for [redacted] months" of Absorb GT1 BVS, therefore, the initial molecular weight ($M_n[0]$ = [redacted] Da) was calculated by substituting k determined from the results of the degradation tests and molecular weight [redacted] Da at the time when the radial strength started declining into $M_n(t) = M_n(0) \exp(-kt)$ and defined as the specification limit.

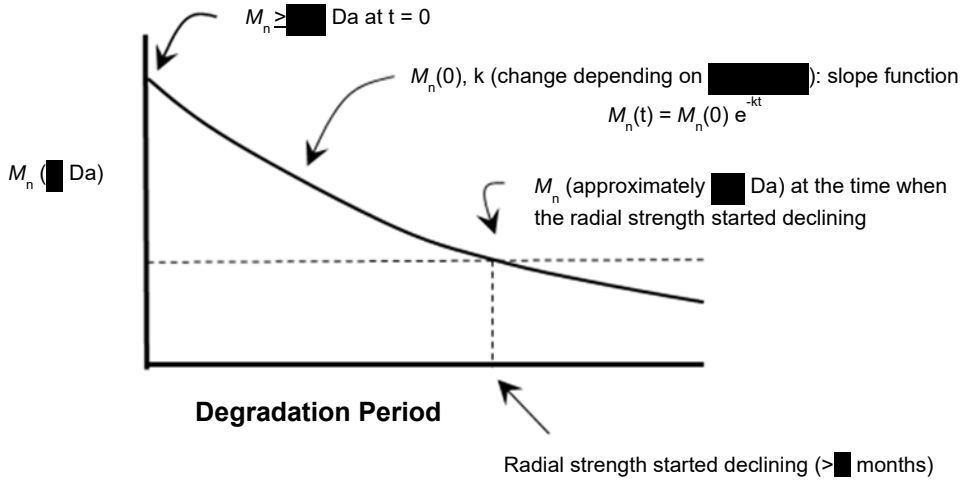


Figure 4. Conceptual graph of initial molecular weight and radial strength

- Justification of the lower limit (initial molecular weight)

The initial radial strength depends on [redacted] but not on [redacted]. As shown in Figure 5, the radial strength decreases only slightly for the first 6 months after M_n reaches [redacted] Da. The radial strength is affected by [redacted], but is maintained for 6 months, which is necessary for completion of endothelialization of the struts, as far as initial M_n is [redacted] Da.

Figure 5. Relationship between radial strength and M_n
(period shown in yellow, 0 to 3 months; period shown in light blue, 6 months after [redacted] Da is reached)

- Range of the specification limit
  An analysis was made on the distribution of M_n of the test sample batches that were manufactured between [redacted] and [redacted] and that were used in the Japanese clinical study (Study AVJ-301) or the US clinical study (ABSORB III study), marketed overseas, or submitted with the present application. The values were in a certain range ([redacted] Da; minimum [redacted] Da, maximum [redacted] Da), indicating the stable quality of the scaffold. Thus, [redacted] Da was defined as the upper limit.

  In conclusion, as far as initial M_n is [redacted] Da, the radial strength can be maintained for 6 months necessary for completion of endothelialization of the struts. This justifies the specification limits of [redacted] to [redacted] Da to assure the efficacy and safety of Absorb GT1 BVS.

2) Absorb GT1 BVS is designed to endure for a certain period of time as a bioresorbable scaffold, unlike conventional non-bioresorbable metal stents designed to have a durable life of at least approximately 10 years. For this reason, the specifications of the scaffold define limits for 2 different clinical periods required, i.e., a period necessary to maintain the vessel lumen (approximately 3 months) and a period necessary for the scaffold to be covered with tissues (approximately 6 months).

   Table 9 presents the specification limits defined for the pulsatile fatigue test where the scaffold is subjected to the fatigue test under accelerated conditions that correspond to pulsations for 3 or 6 months. The justification of these specification limits is described below.

Table 9. Specification limits for pulsatile fatigue test

Time	Specification limit
0 hours (during deployment)	• No fracture is found during deployment. • No scaffold marker loss is found during deployment.
Equivalent to 3 months (10,000,000 cycles)	• No fracture of [redacted] is found. • The number of fractures of [redacted] does not exceed [redacted].
Equivalent to 6 months (20,000,000 cycles)	• No scaffold marker loss is found. • No defect or fracture of [redacted] is found.

(a) 0 hours (during deployment)

These specification limits are appropriate, because another specification assures no scaffold fractures after deployment to the expansion diameter limit, as product performance.

The scaffold skeleton of Absorb GT1 BVS is radiopaque and therefore is not visible under X-ray. For this reason, scaffold markers are essential to identify the position of the implanted Absorb GT1 BVS in clinical use and therefore the absence of scaffold marker loss was defined as a specification limit.

(b) Equivalent to 3 months (10,000,000 cycles)

The specification limits for the first 3 months after scaffold implantation were established based on the clinical requirement that the scaffold should physically maintain the vessel lumen patency for 3 months. The Absorb GT1 BVS scaffold consists of sinusoidal rings that expand circumferentially during balloon inflation. Rings are connected to each other with 3 links. The scaffold's [redacted].

When the scaffold is compressed in the radial direction, [redacted]. The function of the rings and links is maintained for a certain period of time after scaffold implantation. Unless fragments from scaffold damages are lost within [redacted] months after scaffold implantation, up to [redacted] fractures are acceptable at [redacted].

The pulsatile fatigue test revealed the structural discontinuity of [redacted] (fracture of [redacted]) in [redacted] of 24 samples of small-sized and medium-sized scaffold designs. After 20,000,000 cycles (6 months), the structural discontinuity of the scaffold (fracture of [redacted]) was observed at [redacted] sites ([redacted] of 6 samples for small-sized scaffold design, [redacted] of 6 samples for medium-sized scaffold design). After 40,000,000 cycles (12 months), the structural discontinuity of more than one link (fracture of [redacted]) was noted at [redacted] to [redacted] sites per scaffold ([redacted] of 6 samples for small-sized scaffold design, [redacted] of 6 samples for medium-sized scaffold design). However, no [redacted] was observed. These results demonstrated that [redacted].

In summary, the number of fractures of scaffold [redacted] does not contribute to [redacted], justifying the specification limit (The number of fractures of [redacted] does not exceed [redacted]).

(c) Equivalent to 6 months (20,000,000 cycles)

Since 3 months are required to physically maintain the vessel lumen patency in patients treated with Absorb GT1 BVS, the radial strength does not need to be maintained during this period. The results of animal studies indicated completion of strut coverage by neointima at 90 and 180 days after scaffold implantation. The clinical study (ABSORB cohort B using BVS-B, a previous generation of Absorb GT1 BVS) also demonstrated that 98.2% (paired analysis) or 95.8% (non-paired analysis) of the struts became covered with vessel wall tissue at 6 months post-operative as confirmed by OCT. Assuming that the endothelialization of the struts is completed within 6 months, the structural specification established was "No defect or fracture of [redacted] is found."

In addition, to verify the positioning of the implanted Absorb GT1 BVS, the absence of scaffold marker loss was defined as a specification limit.

As a result of review on the justification of the performance and safety specifications, PMDA concluded that the applicant's explanations were reasonable and that there was no particular problem with the proposed specifications.

2.(2) Studies to support device safety

2.(2).1) Physicochemical properties

2.(2).1).A. Summary of the submitted data

The raw materials (PLLA and PDLLA) of the scaffold's skeleton and the coating layer are supplied by 2 companies, [redacted] ([redacted] corporation) and [redacted] ([redacted] corporation). Studies on the physicochemical properties of the raw materials and the scaffold were conducted to confirm the equivalence of the raw materials from the 2 suppliers and the results were submitted in support of the present application. The following data on the physicochemical properties of the raw materials were submitted for equivalence assessment: comparison of the results of acceptance inspection of raw materials, average molecular weight and distribution of molecular weights, structural characterization by ^{1}H-Nuclear Magnetic Resonance (NMR), the ratio of D-lactic acid and L-lactic acid contained in PLA, and crystallinity (scaffold). The scaffold was tested for physicochemical properties. The results of the following parameters were submitted for device characterization: the theoretical value of scaffold-free area, flexibility, and the characteristics of the drug coating (drug content uniformity of the scaffold, drug distribution to the balloon/protective sheath, drug coating adhesion, and drug coating thickness). In addition, the study results on the *in vitro* degradation behavior of the scaffold (M_n, distribution of molecular weights [Polydispersity Index (PDI)], radial strength, and weight loss) were submitted for equivalence assessment. The applicant explained that the characteristics of the extractable substances and the corrosion resistance of the scaffold markers are already known.

2.(2).1).B. Outline of the review conducted by PMDA

PMDA asked the applicant to clarify the following issues on the physicochemical properties:

(a) How does the applicant ensure that the use of the raw materials from the different suppliers does not affect the efficacy and safety of Absorb GT1 BVS?

(b) Were appropriate conditions for the simulation test selected based on the actual situation of the use of Absorb GT1 BVS, in order to assess the degradation characteristics of Absorb GT1 BVS in an *in vitro* degradation behavior study?

The applicant's response:

(a) The equivalence of the raw materials from the 2 suppliers was demonstrated by the tests defined in the specifications of the raw materials, as well as the tests of their physicochemical properties, i.e., average molecular weight and distribution of molecular weights, structural characterization by ^{1}H-NMR, the ratio of D-lactic acid and L-lactic acid contained in PLA, and the scaffold's crystallinity of the final product.

[redacted] is performed during the manufacturing process as a critical test to control the degradation of the scaffold. For the final product, tests for M_n and the radial strength at [redacted] have been defined in the specifications. The same specification limits of the 3 tests for the raw materials have been employed by the suppliers.

An *in vitro* degradation test with the scaffolds manufactured using the raw materials from the 2 supplier was performed to assess the radial strength up to 24 months and the degradation behavior (M_n, PDI, and weight loss) up to 30 months. The use of the raw materials from the different suppliers did not affect the degradation behavior. The applicant confirmed that degradation behavior was equivalent.

(b) This *in vitro* test was conducted in accordance with ISO 13781 "Poly(L-lactide) resins and fabricated forms for surgical implants – *In vitro* degradation testing" and ASTM F1635-11 "Standard Test Method for *in vitro* Degradation Testing of Hydrolytically Degradable Polymer Resins and Fabricated Forms for Surgical Implants."

The degradation (deterioration) of Absorb GT1 BVS progresses as the ester linkage of PLA that constitutes the scaffold skeleton is hydrolyzed. Hydrolysis is a chemical process and is the only mechanism by which the molecular weight of PLA decreases. The extrinsic factors that influence the hydrolysis rate of PLA are water, temperature, and pH. In the *in vitro* degradation test, the test samples were immersed in water controlled at 37°C and pH [redacted] to maintain them in an appropriate physiological condition. In accordance with the third-order kinetic reported by Pitt et al.,[4,5,6] the hydrolysis rate of the PLLA scaffold depends on the ester linkage, water, and the concentration of the terminal carboxyl group, which is produced by hydrolysis. A change in the concentration of water is marginal because water exists in great excess *in vitro* and *in vivo*. The third-order reaction is, therefore, applicable under *in vitro* and *in vivo* conditions. As described later in Section "2.(2).3) Stability and durability," there has been no evidence that the degradation rate of the Absorb GT1 BVS scaffold is influenced by fatigue loading.

PMDA's view:
As a result of review on the equivalence of the scaffold and coating made of the raw materials from the 2 different suppliers, the specifications of the raw materials, and the specifications of the manufacturing process, the use of the raw materials from the different suppliers is considered to minimally affect the quality, efficacy, and safety of Absorb GT1 BVS. The applicant's policy is acceptable.

PMDA also considers that the conditions of the *in vitro* degradation test are acceptable. This is based on the rationale for the conditions of this test (as explained by the applicant) and the study results described in Section "2.(3).2).A.(b) Biodegradation." The degradation characteristics of BVS-B scaffold in the body was assessed in the biodegradation study using porcine coronary arteries, and the change in M_n over time in the study indicated consistency in degradation behavior of the scaffold between the *in vivo* and *in vitro* degradation tests.

2.(2).2) Biological safety

2.(2).2).A. Summary of the submitted data

The applicant submitted the results of the biological safety studies that were conducted in accordance with the "Basic principles of biological safety evaluation required for marketing application for medical devices" (PFSB/ELD/OMDE Notification No. 0301-20 dated March 1, 2012, issued by the Office of Medical Devices Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW), the ISO 10993 series of standards, etc. PLLA and PDLLA for Absorb GT1 BVS are supplied by 2 different suppliers. The applicant explained that evaluation of the biological safety based on the study results with the raw material from either of the 2 suppliers can be justified because the equivalence of the raw materials from these suppliers has been verified [see Section "2.(2).1) Physicochemical properties"] and the amounts of residual monomers (lactide) contained in these materials are considered comparable.

The delivery system of Absorb GT1 BVS was tested for cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, pyrogenicity, and hemocompatibility (hemolysis and coagulation). The submitted data indicated no particular problem.

The scaffold containing no drug was tested for cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, subchronic toxicity/implantation, genotoxicity (reverse mutation, micronucleus, forward mutation, and chromosomal aberration assays), pyrogenicity, and hemocompatibility (hemolysis, complement activation, and coagulation). The scaffold containing the drug was tested for cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, genotoxicity (reverse mutation, micronucleus, forward mutation, and chromosomal aberration assays), pyrogenicity, and hemocompatibility (hemolysis, complement activation, and coagulation). The partial thromboplastin time in the hemocompatibility (coagulation) test showed a significant difference in the coagulation time between the test article and the negative control. The applicant, however, considered that the hemocompatibility of the Absorb GT1 BVS scaffold was unlikely to pose any clinical problem, for the following reasons: (i) The difference between the test article and the negative control was not numerically large, (ii) the prothrombin time for the test article was comparable to that for the negative

control, and (iii) the animal studies indicated no risk for thrombosis. Other studies submitted showed no particular problem.

According to the applicant, the biological safety of the scaffold was also evaluated in animal studies. Hemocompatibility (thrombosis) (samples with and without the drug), subacute and subchronic/chronic systemic toxicity, and implantation (samples with the drug) are described in Section "2.(3).2) Animal studies." The chronic toxicity, carcinogenicity, reproductive and developmental toxicity (samples with and without the drug), and biological safety of degradation products of the scaffold were evaluated based on the fact that the Absorb GT1 BVS scaffold contains the same drug (everolimus) as that of XIENCE V and considering other product made from PLLA or PDLLA.

2.(2).2).B. Outline of the review conducted by PMDA

As a result of review on the data related to the biological safety of Absorb GT1 BVS, PMDA concluded that the applicant's explanations were reasonable and that there was no particular problem with the biological safety of Absorb GT1 BVS.

2.(2).3) Stability and durability

2.(2).3).A. Summary of the submitted data

The stability of the delivery system was investigated using materials that have not been used in approved products. A stability study (catheter shaft pressure resistance, proximal marker locations, and tensile strength at the proximal junction) was conducted using 6-month real-time aged samples and 18-month accelerated aged samples. The submitted study results demonstrated that all of the samples conformed to the specifications.

The stability (mechanical properties) of the scaffold was assessed using samples stored at ≤25°C for 12 months. The samples were tested for scaffold percent recoil (at nominal pressure and post-dilatation), scaffold deployment uniformity, percent change in scaffold length from pre- to post-expansion (at nominal pressure and post-dilatation), scaffold radial strength (at nominal pressure and post-dilatation), scaffold expansion diameter limit, scaffold movement (distal and proximal directions), nominal pressure, particulate matter, and scaffold coating integrity. The samples conformed to the specification limits of all of these tests. To assess the stability (other than mechanical properties) of the scaffold, samples stored under long-term conditions (6 and 12 months), those stored under accelerated conditions (6 months), those stored under long-term and stressed conditions (6 months), and those stored under the conditions that meet the requirements of the ICH Q1B [redacted] (photostability) were tested for total drug content, drug release, the amounts of impurities and degradation products, and M_n of the scaffold. The samples conformed to the specification limits of all of these tests.

The potential deterioration of Absorb GT1 BVS caused by [redacted] sterilization was also investigated. This sterilization method was shown not to profoundly affect the efficacy and safety of Absorb GT1 BVS.

On the basis of the above results, a shelf life of 12 months has been proposed for Absorb GT1 BVS when stored at ≤25°C (at the upper temperature limit of 30°C for ≤6 hours).

To assess the durability of the scaffold, samples were subjected to analyses for stress and fatigue stress during the acute phase (during crimping and placement) based on the finite element analysis method. The scaffold was shown to endure physiological loads. The pulsatile durability of scaffolds in an overlapping configuration was also assessed in fatigue studies and characterization studies for particulates under accelerated fatigue conditions. None of the studies demonstrated any particular problem with the pulsatile durability of the scaffold.

2.(2).3).B. Outline of the review conducted by PMDA

PMDA asked the applicant to provide the justification for the proposed shelf life because the stability study of the scaffold showed a decrease in radial strength over time.

The applicant's response:

[redacted]

The scaffold of Absorb GT1 BVS is characterized by [redacted]. PLLA used in Absorb GT1 BVS [redacted] exceeded its specification limit (≥350 mmHg).

The results of the performance study, etc. submitted in support of the present application showed that the radial strength (at nominal pressure and expansion diameter limit) and damaged scaffold diameter (inner diameter of the scaffold when it is broken by continued inflation) after sterilization was [redacted] were assessed in the pulsatile fatigue test and shown to conform to the proposed specifications.

In the ABSORB III study, a total of 1482 scaffolds were implanted and the relationship between [redacted] and adverse events (target lesion failure [TLF] and stent thrombosis [ST]) was investigated. The study demonstrated [redacted]. Adverse events (TLF and ST) occurred with 110 of 1482 scaffolds implanted, but

[redacted] was not observed. These adverse events (TLF and ST) were not noted [redacted] investigational device (a total of 10).

The above results justify the proposed shelf life of 12 months.

On the basis of the applicant's explanation, PMDA concluded that the proposed shelf life of 12 months is acceptable. However, the radial strength of Absorb GT1 BVS [redacted] was [redacted] mmHg, substantially exceeding the lower specification limit of 350 mmHg. PMDA asked the applicant to reconsider the specification limit of the radial strength.

The applicant's response:
The proposed [redacted] of the radial strength in [redacted] is [redacted] mmHg. [redacted] is conducted. This value is the lower limit of the radial strength that was statistically determined using the historical stability data and an exponential decay model to assure the specification during the shelf life. Although the statistically calculated radial strength is [redacted] mmHg, a more conservative value of [redacted] mmHg has been proposed.

PMDA asked the applicant to specify [redacted] of the radial strength in [redacted] and the applicant agreed.

Since the pulsatile fatigue test of Absorb GT1 BVS was conducted under accelerated conditions, PMDA also asked the applicant to explain the appropriateness of the accelerated conditions, by clarifying whether the test had been conducted under conditions that simulated the use of Absorb GT1 BVS in clinical settings.

The applicant's response:
Increased temperatures accelerate the degradation of PLA. The relationship between the degradation rate constant and the temperature is described by the Arrenius equation. The activation energy in the equation has been determined experimentally. Since the hydrolytic reaction rate of the ester linkage of PLA depends on temperature,[7] increased temperatures accelerate hydrolytic cleavage of the ester bond of PLLA and PDLLA. The pulsatile fatigue test of the Absorb GT1 BVS scaffold was conducted at the frequency of radial pulsation of [redacted] Hz and the hydrolysis temperature of [redacted]°C to achieve [redacted]-fold mechanical acceleration and degradation rate.

In the pulsatile fatigue test, M_n and the radial strength of the scaffold were also measured in an ancillary manner. M_n and the radial strength were comparable from [redacted] through [redacted] months under the *in vitro* degradation test conditions and the pulsatile fatigue conditions. There is no evidence that the degradation of the scaffold was accelerated under pulsatile fatigue conditions compared with the *in vitro* degradation test conditions.

PMDA accepted the applicant's explanation. As a result of review on the data related to stability and durability, PMDA concluded that there was no particular problem with the stability and durability of Absorb GT1 BVS.

2.(3) Studies to support device performance

The applicant submitted the results of the design verification test and animal studies to support the performance of Absorb GT1 BVS.

2.(3).1) Design verification test

2.(3).1).A. Summary of the submitted data

In the design verification test, AVJ-301 having the same scaffold as that of Absorb GT1 BVS was tested for the following: scaffold percent recoil (at nominal pressure and post-dilatation); uniformity of scaffold expansion; percent change in scaffold length from pre- to post-expansion (at nominal pressure and post-dilatation); scaffold radial strength (radial force) (at nominal pressure and post-dilatation); scaffold expansion diameter limit; drug identity (ultraviolet-visible spectrophotometry and liquid chromatography); total drug content, drug content uniformity; drug release; the amounts of residual solvents, impurities, and degradation products; scaffold coating integrity; scaffold's M_n; MRI compatibility; scaffold movement; pullback into guiding catheter; nominal pressure; inner member collapse; maximum guide wire diameter; radial strength (radial force) at [redacted]; and crossing profile. The submitted results of these tests demonstrated that the test samples conformed to the specifications.

Absorb GT1 BVS was also tested for catheter preparation, balloon inflation/deflation times, maximum inflation pressure, tensile strength (catheter, proximal junction, and soft tip), catheter shaft pressure resistance, balloon fatigue, particulate matter, hydrophilic coating (adhesion and friction coefficient of coating), radiopacity, bacterial endotoxins, and catheter kink, flexibility, delivery performance, and torque. The submitted results of these tests showed that the samples conformed to the specifications or were comparable to the conventional product.

2.(3).1).B. Outline of the review conducted by PMDA

As a result of review on the data from design verification test, PMDA concluded that there was no particular problem with the design verification of Absorb GT1 BVS.

2.(3).2) Animal studies

2.(3).2).A. Summary of the submitted data

Table 10 presents the animal studies of Absorb GT1 BVS.

Table 10. Study design

Study	Investigational device (control)	Investigational device size (No. of samples*)	Animal species** (No. of animals*)	Follow-up period	Endpoint
(a) Pharmacokinetics					
PK (BVS-B)	BVS-B (None)	3.0 × 18 mm (7-9)	FS (3)	3 hours, 1, 3, 7, 14, 28, 60, and 90 days	• Drug release • Drug concentration in arterial tissue • Drug concentration in blood • Drug concentration in critical organs (myocardium, lungs, liver, spleen, and kidneys)
PK (AVJ-301)	AVJ-301 (None)	3.0 × 18 mm (6-8)	FS (3)	3 hours, 1, 3, 7, 14, 28, 60, and 90 days	
PK (AVJ-301)	AVJ-301 (None)	3.0 × 18 mm (6-8)	FS or YS (3-4)	3 hours, 1, 3, 7, 14, 28, 60, 90, 120, 180, and 300 days	
(b) Degradation					
Degradation	BVS-B (None)	3.0 × 12, 18 mm (8-12)	FS or YS (3-6)	28, 90, and 180 days 12, 18, 24, 30, 36, and 42 months	• Mortality and incidence • Characterization of degradation of polymer • Safety
(c) Safety (single implantation)					
Sub-chronic, chronic	AVJ-301 (XIENCE V)	3.0 × 18 mm (12)	FS or YS (9-10)	28, 90, and 180 days	• Mortality and incidence • QCA (TIMI flow) • Histomorphology • Histomorphological measurements • SEM • OCT • IVUS
Acute, sub-chronic, chronic	BVS-B (XIENCE V)	3.0 × 12, 18 mm (12-21)	FS or YS (7-13)	28, 90, and 180 days 12, 18, 24, 30, 36, 42, and 48 months	
(d) Safety (overlapping implantation)					
sub-acute, sub-chronic	BVS-B (XIENCE V)	3.0 × 12 mm (12 pairs)	FS (8-9)	28 and 90 days	• Mortality and incidence • QCA (TIMI flow) • Histomorphology • Histomorphological measurements • SEM (28, 90 days) • OCT • IVUS (12 months)
Chronic	AVJ-301 (XIENCE V)	3.0 × 12 mm (15 pairs)	YS (12)	12 months	

* Number of the products (samples) implanted for each follow-up period and number of animals used
** FS = domestic pig, YS = Yucatan miniature pig

(a) Pharmacokinetics

The PK following implantation of Absorb GT1 BVS was evaluated in a porcine coronary artery model. The study demonstrated the bioequivalence of the drug release profile between BVS and XIENCE stents. The everolimus concentration in the scaffold-implanted vascular tissue remained constant from [redacted] to 28 days post-implantation. This result indicated that Absorb GT1 BVS maintained effective concentrations to prevent vascular reaction of the implanted blood vessel (neointimal hyperplasia) and help vascular healing (endothelialization). The duration of exposure of the myocardium to the drug was <14 days. Only a trace amount of the drug was distributed to the critical organs (lungs, liver, kidneys, and spleen) other than the implanted site.

(b) Biodegradation

The degradation of BVS at 28 days through 42 months post-implantation was characterized in the porcine coronary artery model. The degradation behavior of the investigational device in the porcine animal study was consistent with that in the separate *in vitro* degradation behavior test. The scaffold was

biodegraded through hydrolysis. The degradation and absorption of the polymer were completed in approximately 36 months.

(c) Safety evaluation (single implantation)

The safety of BVS was evaluated at 3 days through 48 months post-implantation using XIENCE stent as the control. Both BVS and control groups met the acceptance criteria for all endpoints at all timepoints. On the other hand, BVS tended to be associated with a higher inflammation score than XIENCE at ≥180 days although BVS met the acceptance criterion. BVS also had a higher percent calcification, which was measured for device characterization, than XIENCE stent at all timepoints through 28 days.

(d) Safety evaluation (overlapping implantation)

The safety of BVS was evaluated at 28 and 90 days, and 12 months following implantation of overlapping BVS versus overlapping XIENCE. Both BVS and control groups met the acceptance criteria for all endpoints at all timepoints. BVS had a higher percent calcification, which was measured for device characterization, than XIENCE stent at all timepoints through 28 days.

2.(3).2).B. Outline of the review conducted by PMDA

The submitted animal studies demonstrated that BVS tended to be associated with a higher inflammation score than XIENCE for a certain period of time. PMDA asked the applicant to explain the safety of Absorb GT1 BVS by describing how this finding was interpreted.

The applicant's response:

In the single implantation studies, the BVS group tended to have a higher intimal inflammation score than the XIENCE group for a certain period of time, but met the acceptance criterion throughout the entire study period (mean score <2[i]).

The BVS group had no adverse findings in the implanted blood vessels at any timepoints including those at which a higher inflammation score was noted (12 and 18 months post-procedure) and had benign neointimal coverage of the struts. In particular, the media and adventitia of a majority of the observed blood vessels were intact. An exception was the rare occurrence of implantation-related mechanical injury observed in both BVS and XIENCE groups. Host-specific inflammation, which is not rare in animal models, was also observed.[8,9,10,11,12] The aggregation of macrophages and multinucleated giant cells around the struts, which was seen only temporarily, was considered to have resolved based on the decreased incidence of inflammatory reaction during the chronic period.

The inflammation score is affected by variability among individual animals. For example, a test animal had inflammatory reaction in all of the 3 coronary arteries after implantation for 12 and 18 months. The increased mean inflammation score was noted when the allocation ratio was 2:1 (or less) for the BVS group versus the XIENCE group. The BVS group had no similar host-dependent reaction after 24-month single implantation. This suggests that the inflammation score was lower at 24 months than at 12 and 18 months. In the 12-month overlapping implantation study, the BVS group tended to have a low inflammation score, which was comparable to that in the XIENCE group.

[i] This was defined based on the results (BMS and DES) of a previous study.

The inflammation observed in the BVS group appeared to be not attributable to the degradation of the scaffold. The inflammation score peaked at 12 months and then decreased, while the weight loss of the scaffold rapidly progressed from [redacted] months to [redacted] months. During this period, the inflammation score was low, conforming to the safety criteria.

PMDA's view:
Although BVS tended to be associated with a high inflammation reaction score for a certain period of time, inflammation did not tend to worsen chronically and the clinical studies showed no clinically intolerable adverse events associated with inflammation. For these reasons, PMDA accepted the applicant's opinion that the data support the safety of Absorb GT1 BVS.

The percent calcification with BVS was higher than that with XIENCE. PMDA asked the applicant to explain the safety of Absorb GT1 BVS, taking this finding into account.

The applicant's response:
For the following reasons, most BVS-related calcification cases appeared to be benign mineral deposition attributable to the coating (PDLLA-everolimus) of Absorb GT1 BVS[13]:

- The amount of calcification itself was small and calcification was observed throughout the entire follow-up period.
- Calcification was localized to the area adjacent to or in close proximity to the struts, mainly at their vascular wall side and little on their inner surface.
- Calcification contained slightly basophilic granules. Most of the calcified site had a thickness of [redacted] to <[redacted] μm and existed around the struts. The mineral depositions in tissue sections showed secondary enlargement of artifacts due to artifacts specific to tissue contracture associated with dehydration. The calcified area in the tissue sections looked larger than the area actually seen *in vivo*.

The location (surrounding of the struts) and shape (linear distribution) of calcification suggest the involvement of the PDLLA coating in calcification. Similar calcification was identified in animal studies of other products manufactured using bioresorbable polymers.[14,15] No findings suggesting the contribution of PLLA scaffold skeleton and its degradation to calcification have been observed at any timepoint.

Although the mechanism of calcification around the BVS struts remains unknown, comparison of vascular reaction between BVS and XIENCE stent revealed no calcification-related adverse events such as excessive fibrin deposition and inflammatory reaction, at any timepoint, suggesting that the calcification observed with this investigational device was benign.[14]

To prove that the calcification observed in this study does not affect clinical safety, plaque compositions can be identified by intravascular ultrasound virtual histology (IVUS-VH), which is an intravascular ultrasound (IVUS) technique that can analyze plaques quantitatively and qualitatively. IVUS-VH differentiates calcified component and necrotic component of tissue covering the BVS struts. These results can, therefore, be used as surrogate markers.[16] If calcification possibly attributable to the raw

materials of BVS is an adverse effect, the amount of calcified component is expected to increase over time. In the clinical study (ABSORB cohort A using BVS-A and ABSORB cohort B using BVS-B [previous generations of Absorb GT1 BVS]), IVHS-VH at 6, 12, 24, and 36 months post-implantation demonstrated attenuated signals of calcified component, indicating a significant decrease in percent calcification over 36 months post-implantation ($P < 0.05$).[16,17,18,19]

The percent calcification reported by [redacted] corporation was submitted in the present application. It was calculated simply by [redacted] and does not necessarily reflect the degree of calcification. The applicant scored the degree of mineral deposition (calcification). The amount of calcification itself was small at all timepoints as with XIENCE V. Calcification did not involve the neointima adjacent to the struts.

The calcification observed with BVS was attributable to the biological materials. No calcification-related adverse events, such as excessive fibrin deposition and inflammatory reaction, were reported. In conclusion, the data support the safety of Absorb GT1 BVS.

PMDA's view:
The applicant has claimed that the data support the safety of Absorb GT1 BVS because the amount of calcification itself was small and the percent calcification significantly decreased over 36 months post-implantation. The applicant's claim is acceptable, based on the comments from the Expert Discussion.

PMDA accepted the applicant's explanation. As a result of review on the data related to the animal studies, PMDA concluded that there was no particular problem with the results from the animal studies of Absorb GT1 BVS.

2.(4) Studies to support the method of use

The delivery and deployment of Absorb GT1 BVS were evaluated in the animal studies. The safety of Absorb GT1 BVS was also evaluated in the cases where bailout procedures were required during and after the deployment procedure. Absorb GT1 BVS was evaluated or discussed for the following 3 cases: 1) bailout procedures during the implantation, 2) early bailout procedures up to [redacted] months post-implantation, and 3) late bailout procedures after [redacted] months post-implantation.

For assessment of bailout procedures during the implantation, an *in vitro* test of overlapping implantation of BVS and DES or 2 BVSs was conducted, indicating [redacted].

Assessment of early bailout procedures up to [redacted] months post-implantation suggested that overlapping implantation of BVS and DES before completion of endothelialization, i.e., within [redacted] months post-implantation, enabled [redacted]
and that luminal support was supplemented by overlapped DES.

In assessment of late bailout procedures after [redacted] months post-implantation, it was concluded that bailout procedures would not dislocate Absorb GT1 BVS since the animal studies and the clinical study (ABSORB cohort B study using BVS-B [previous generations of Absorb GT1 BVS]) demonstrated the coverage of struts by the vessel wall at [redacted] months post-implantation.

2.(4).B Outline of the review conducted by PMDA

Absorb GT1 BVS is gradually hydrolyzed, leading to a decrease in the strength of the scaffold. Bailout procedure with a metal stent or balloon catheter before endothelialization of the scaffold may result in risks such as scaffold rupture and distal embolism caused by fragments of the scaffold. PMDA asked the applicant to clarify risks associated with additional interventions.

The applicant's response:

To investigate risks associated with bailout procedures for a degraded scaffold, pulsatile fatigue of overlapped BVSs under conditions equivalent to pulsations for [redacted] months was investigated. In addition, BVS that had been implanted in a mock blood vessel and degraded *in vitro* for [redacted] months was tested to determine the passage of devices that are expected to be used for bailout procedures (guide wire, balloon catheter, and XIENCE stent) and the pattern of BVS fracture resulting from overexpansion due to overlapping implantation of XIENCE stent. The devices that were expected to be used for bailout procedures for BVS passed through the artery without any problem. Dilatation by XIENCE stent caused no distortion of BVS, marker loss, or fragmentation.

The above findings appear to support the safety of bailout procedures within [redacted] post-implantation.

PMDA's view:

Given the characteristics of Absorb GT1 BVS, the 3-stage safety evaluation of Absorb GT1 BVS is reasonable. The clinical safety of bailout procedures is to be evaluated also based on the information described in Section "6.B.1.(3) Safety of additional interventions."

3. Conformity to the requirements specified in Paragraph 3 of Article 41 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics

3.A. Summary of the submitted data

The applicant submitted a Declaration of Conformity which states that the product conforms to the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (hereinafter referred to as the "Essential Principles") (MHLW Ministerial Announcement No. 122 of 2005), and to the Ministerial Ordinance on Quality Management System for Medical Devices and In-vitro Diagnostics (MHLW Ministerial Ordinance No. 169 of 2004).

3.B. Outline of the review conducted by PMDA

PMDA concluded that there are no particular problems with the conformity of Absorb GT1 BVS to the Essential Principles.

4. Risk management

4.A. Summary of the submitted data

The applicant submitted a summary of risk management, the risk management system, and its implementation status in reference to ISO 14971 “Medical devices - Application of risk management to medical devices.”

4.B. Outline of the review conducted by PMDA

PMDA reviewed the document on risk management and concluded that there was no particular problem.

5. Manufacturing process

5.A. Summary of the submitted data

The applicant submitted data related to the in-process tests and data related to the sterilization method of Absorb GT1 BVS.

5.B. Outline of the review conducted by PMDA

PMDA reviewed the data on manufacturing process and concluded that there was no particular problem.

6. Clinical data or alternative data accepted by Minister of Health, Labour and Welfare

The applicant submitted the results of the following clinical studies to evaluate the efficacy and safety of Absorb GT1 BVS as attached documents: Japanese Study AVJ-301 using AVJ-301, US ABSORB III study, and the PK study in the ABSORB III study. The applicant also submitted the results of a series of clinical studies of products related to Absorb GT1 BVS (Cohorts A and B in the ABSORB study, the ABSORB EXTEND study, the ABSORB II study, the ABSORB China study) as reference data.

Table 11 presents the design, investigational device, control device, and countries where studies were conducted.

Table 11. Investigational device, control device, and country where studies were conducted

Study	Study design (No. of subjects)	Investigational device (No. of subjects)	Control device (No. of subjects)	Country
Study AVJ-301	Randomized, controlled, non-inferiority study (N = 400)	AVJ-301 (N = 266)	XIENCE PRIME XIENCE Xpedition (N = 134)	Japan
ABSORB III clinical study	Randomized, controlled, non-inferiority study (N = 2008)	AVJ-301 (N = 1322)	XIENCE V XIENCE PRIME XIENCE Xpedition (N = 686)	US, Australia
ABSORB III pharmacokinetics study	Open-label study (N = 12)	AVJ-301 (N = 12)	-	US
ABSORB Cohort A	Single-arm study (N = 30)	BVS-A (N = 30)	-	The Netherlands and other 3 countries
ABSORB Cohort B	Single-arm study (N = 101)	BVS-B (N = 101)	-	The Netherlands and other 7 countries
ABSORB EXTEND clinical study	Single-arm study (N = 812, including 40 Japanese subjects)	BVS-B AVJ-301 (N = 812)	-	India and other 25 countries
ABSORB II clinical study	Randomized, controlled study (N = 501)	BVS-B AVJ-301 (N = 335)	XIENCE PRIME (N = 166)	Italy and other 13 countries
ABSORB China clinical study	Randomized, controlled study (N = 480)	AVJ-301 (N = 241)	XIENCE V (N = 239)	China

6.A. Summary of the submitted data

6.A.(1) Study AVJ-301 (study period, April 2013 to [redacted] 2019 [planned])

Study AVJ-301 is a prospective, randomized, active-controlled, single-blind, multicenter, non-inferiority study which was conducted in Japanese clinical sites to evaluate the efficacy and safety of AVJ-301 versus approved DESs in the treatment of patients with ischemic heart disease who had ≤2 *de novo* native coronary artery lesions and who were candidates for elective percutaneous coronary intervention (PCI). This study was conducted using XIENCE PRIME and XIENCE Xpedition, which are approved DESs with the same drug as Absorb GT1 BVS, as active controls at 38 study sites in Japan (target sample size, 400 subjects [267 in the BVS group, 133 in the XIENCE group]).

Subjects were randomized to one of imaging subgroups according to the type and timing of intravascular diagnostic imaging: the IVUS subgroup, the OCT 1 subgroup, or the OCT 2 subgroup. The IVUS subgroup underwent IVUS at immediate post-procedure and 3-year follow-up. The OCT 1 subgroup underwent OCT at immediate post-procedure and 2-year and 3-year follow-ups, and the OCT 2 subgroup only at 3-year follow-up (Figure 6). At selected study sites, substudies were also conducted for re-stenosis assessment by multi-slice computed tomography (MSCT) at 13-month and 3-year follow-ups or vascular reaction assessment by acetylcholine (ACh) provocation test at 4-year follow-up. Subjects

were allocated to the BVS or XIENCE group, taking into consideration diabetes and the number of target lesions as important prognostic factors that might influence study results.

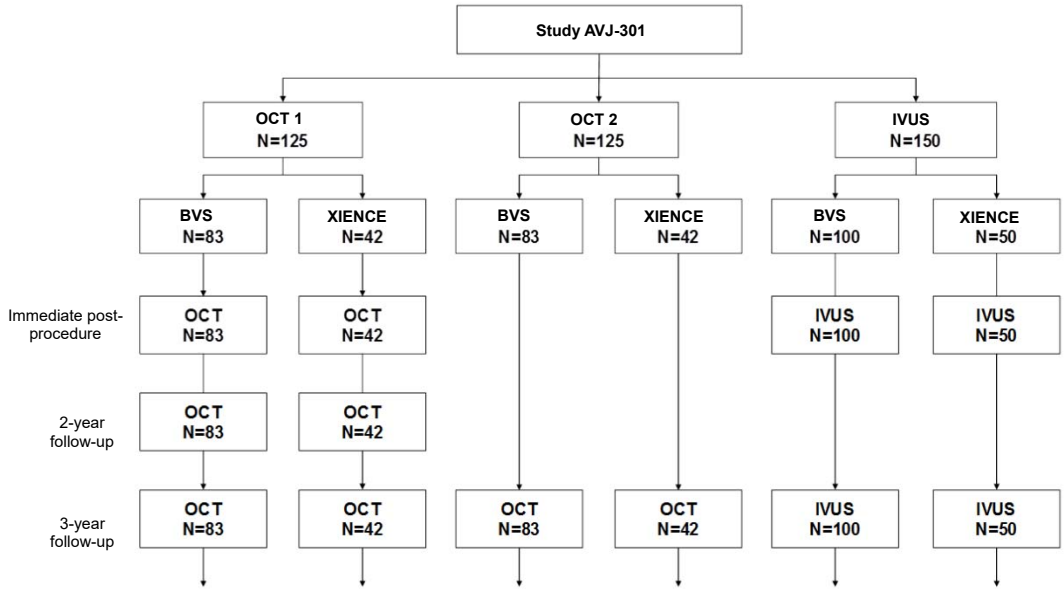


Figure 6. Allocation and timing of intravascular diagnostic imaging

Patients aged ≥20 years who met all of the following key inclusion criteria were included in the study:

(a) having 1 *de novo* lesion (target) in a coronary artery or 2 *de novo* lesions (2 target, or 1 target and 1 non-target) in separate coronary arteries (note that a lesion located at ≥5 mm from a previously treated lesion in the same branch was defined as a *de novo* lesion),

(b) having a target lesion(s) in a native coronary artery with percent diameter stenosis (%DS) of ≥50% and <100% as visually estimated and a blood flow of TIMI Grade ≥1, and

(c) having a target lesion(s) in a native coronary artery with a maximum vessel diameter of ≥2.5 and ≤3.75 mm at a planned device implantation site and a target lesion length of ≤24 mm as visually estimated.

The key exclusion criteria for angiography are as follows:

(a) lesion not treatable by balloon angioplasty (e.g., severely calcified lesion);

(b) lesion to which the study device cannot be delivered because of extreme angulation of ≥90° or excessive tortuosity proximal to the target lesion;

(c) lesion located in the left main artery or within 3 mm of the aorta junction;

(d) lesion involving a bifurcation with side branch ≥2 mm in diameter or side branch requiring pre-dilatation.

(e) lesion involving myocardial bridging or a bypass graft, or thrombotic lesion.

Subjects were scheduled to undergo follow-up at pre-procedure and immediate post-procedure, during hospitalization, and at 1 and 6 months, 1, 2, 3, 4, and 5 years post-procedure.

The primary endpoints of this study were the incidence of TLF at 12 months post-procedure, defined as the composite of cardiac death, target vessel myocardial infarction (TV-MI), and ischemia-driven target lesion revascularization (ID-TLR). On the assumption that the (true) incidence of TLF at 12 months was 9% in the BVS and XIENCE groups and that the non-inferiority margin (δ) was 8.6%, 390 subjects (260 in the BVS group and 130 in the XIENCE group) were needed to reject the null hypothesis ($H_{0,}$ $TLF_{BVS} - TLF_{XIENCE} \geq \delta$) at the allocation ratio of 2:1 for the BVS group versus the XIENCE group and the one-sided significance level (α) of 0.05. With this sample size, the power of 90% was calculated by Farrington-Manning test. Allowing for the dropout rate of 2.5%, the target sample size of 400 subjects (267 in the BVS group and 133 in the XIENCE group) was selected.

The secondary endpoints of this study were in-segment late lumen loss determined by quantitative coronary angiography (QCA) at Month 13, a change in mean in-stent or in-scaffold vessel diameter before and after administration of nitrate for QCA at 3 years, and a change in mean in-stent or in-scaffold lumen area determined by IVUS at 3 years (powered secondary endpoints), and re-stenosis by MSCT at 13 months (health economic evaluation endpoint). Other secondary endpoints assessed in the study were acute success (device success and procedural success), death (cardiac death, vascular death, and non-cardiac death), myocardial infarction (MI), Q-wave myocardial infarction (QMI), non Q-wave myocardial infarction (NQMI), target lesion revascularization (TLR), ID-TLR, non-ischemia-driven target lesion revascularization (NID-TLR), target vessel revascularization (TVR), ischemia-driven target vessel revascularization (ID-TVR), non-ischemia-driven target vessel revascularization (NID-TVR), all coronary revascularization, composite endpoint of major adverse cardiac event (MACE) (death/MI, cardiac death/MI, TLF, cardiac death/MI/ID-TLR), target vessel failure (TVF) (cardiac death/MI/ID-TLR/ID-TVR [non-target lesion]), death/MI/coronary revascularization (death, myocardial infarction and revascularization [DMR]), and ST during hospitalization, and at 1, 6, and 12 months, and 2, 3, 4, and 5 years post-procedure. In addition, the following imaging endpoints were selected: angiographic endpoints at immediate post-procedure, and 13 months and 2, 3, and 4 years; and vascular reaction after administration of nitrate at 2 and 3 years, as well as the aforementioned imaging endpoints including vascular reaction after ACh administration, IVUS endpoints, OCT endpoints, and MSCT endpoints.

The intention to treat (ITT) population was used for statistical analyses of the primary and secondary endpoints excluding the imaging endpoints. The ITT population included all subjects enrolled in Study AVJ-301 regardless of whether they received the study device.

In analyses of the clinical endpoints including the primary endpoints, subjects whose treatment or assessment was censored by each follow-up timepoint were excluded from the analysis parameter for that timepoint to avoid underestimating the incidence of each event. However, subjects with known DMR were included in the analysis parameter. At follow-up timepoints through 12 months, 265 subjects in the BVS group and 133 subjects in the XIENCE group were evaluable (Figure 7).

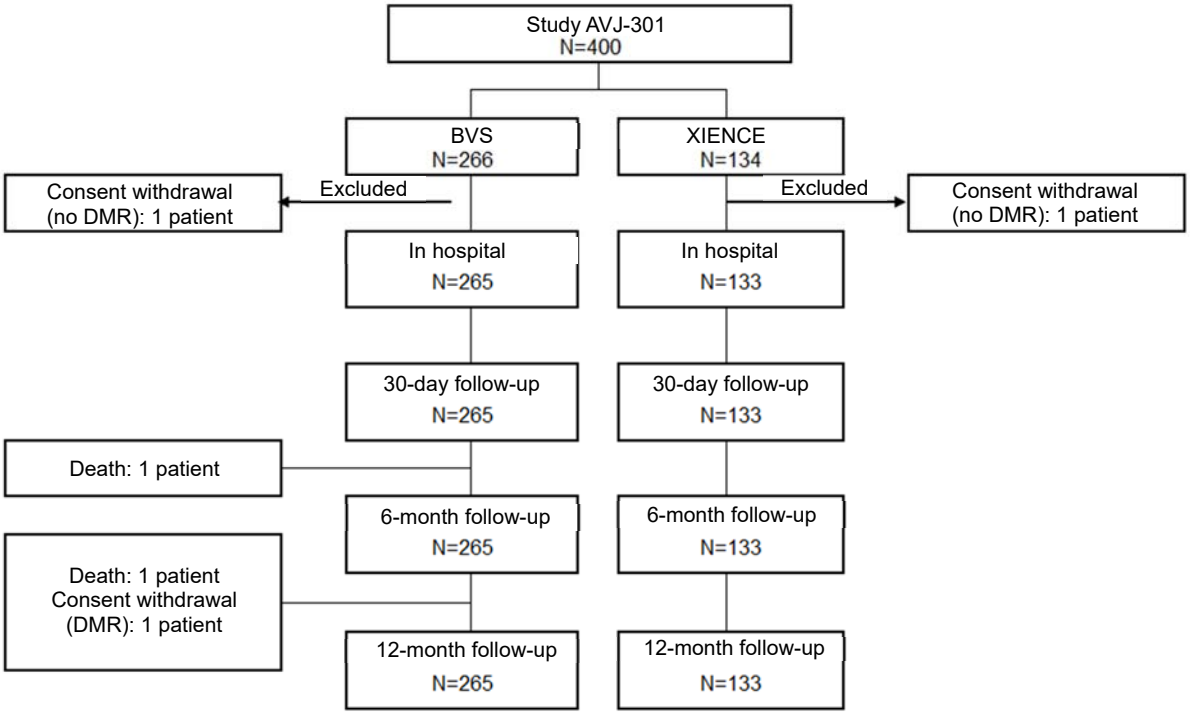


Figure 7. Data sets for clinical endpoint analysis (ITT analysis)

Table 12 presents baseline subject characteristics. Table 13 presents baseline lesion characteristics. There was no significant difference in any of these characteristics between the 2 groups.

Table 12. Baseline demographic and clinical characteristics (ITT analysis)

	BVS (N = 266)	XIENCE (N = 134)	Difference [95% CI][1]
Subject characteristics			
Age (year)	67.1 ± 9.4 (266)	67.3 ± 9.6 (134)	−0.1 [−2.1, 1.9]
Men	78.9% (210/266)	73.9% (99/134)	5.07% [−3.47%, 14.26%]
Body Mass Index (kg/m^2)	24.01 ± 3.03 (260)	24.27 ± 2.96 (130)	−0.26 [−0.89, 0.37]
Current smoker	19.9% (53/266)	21.6% (29/134)	−1.72% [−10.57%, 6.33%]
Hypertension	78.2% (208/266)	79.9% (107/134)	−1.66% [−9.63%, 7.18%]
- Requiring medication	72.2% (192/266)	73.1% (98/134)	−0.95% [−9.80%, 8.56%]
Dyslipidaemia	82.0% (218/266)	82.1% (110/134)	−0.13% [−7.66%, 8.32%]
- Requiring medication	74.1% (197/266)	79.1% (106/134)	−5.04% [−13.26%, 4.04%]
Diabetes mellitus	36.1% (96/266)	35.8% (48/134)	0.27% [−9.80%, 9.93%]
- Requiring medication	31.2% (83/266)	29.9% (40/134)	1.35% [−8.41%, 10.52%]
- Requiring insulin	9.0% (24/266)	8.2% (11/134)	0.81% [−5.75%, 6.21%]
HbA1c (%)	6.23 ± 1.06 (265)	6.15 ± 0.78 (133)	0.09 [−0.10, 0.27]
Prior coronary revascularization	36.1% (96/266)	38.1% (51/134)	−1.97% [−12.07%, 7.81%]
- Target vessel	3.4% (9/266)	5.2% (7/134)	−1.84% [−7.25%, 2.12%]
History of MI	16.0% (42/262)	23.9% (32/134)	−7.85% [−16.67%, 0.25%]
Family history of juvenile coronary artery disease	6.5% (16/246)	8.1% (10/124)	−1.51% [−8.13%, 3.76%]
Ischemic findings at enrollment			
Stable angina	9.8% (26/266)	65.7% (88/134)	−1.76% [−11.33%, 8.28%]
Unstable angina	63.9% (170/266)	16.4% (22/134)	−6.64% [−14.44%, 0.11%]
Asymptomatic ischemia	26.3% (70/266)	17.9% (24/134)	8.41% [−0.45%, 16.30%]

[1] Confidence intervals (CIs) were calculated by normal approximation for differences in continuous variables and by Newcombe scoring method for categorical variables. (Hereinafter, CIs are calculated in the same manner, unless otherwise stated.)

Note 1) N = total number of enrolled subjects (hereinafter, the same applies unless otherwise stated)

Table 13. Baseline lesion characteristics (ITT analysis)

	BVS (N = 266) (L = 275)	XIENCE (N = 134) (L = 137)	Difference [95% CI]
Number of target lesions			
Mean number of target lesions	1.0 ± 0.2 (266)	1.0 ± 0.1 (134)	0.0 [−0.0, 0.0]
1 target lesion	96.6% (257/266)	97.8% (131/134)	−1.14% [−4.42%, 3.29%]
2 target lesions	3.4% (9/266)	2.2% (3/134)	1.14% [−3.29%, 4.42%]
Target vessel			
LAD	46.2% (127/275)	42.3% (58/137)	3.85% [−6.34%, 13.75%]
LCX	22.9% (63/275)	26.3% (36/137)	−3.37% [−12.54%, 5.15%]
RCA	30.9% (85/275)	31.4% (43/137)	−0.48% [−10.16%, 8.68%]
Lesion morphology			
Calcified (moderate or severe)	27.7% (76/274)	32.8% (45/137)	−5.11% [−14.73%, 4.08%]
Tortuous (moderate or severe)	8.4% (23/274)	8.0% (11/137)	0.36% [−6.03%, 5.59%]
Eccentric	81.7% (223/273)	82.5% (113/137)	−0.80% [−8.21%, 7.53%]
Thrombus	0.0% (0/274)	0.0% (0/137)	0.00% [−2.73%, 1.38%]
ACC/AHA lesion classification			
A	4.0% (11/275)	3.6% (5/137)	0.35% [−4.58%, 4.02%]
B1	20.0% (55/275)	20.4% (28/137)	−0.44% [−9.10%, 7.38%]
B2	56.0% (154/275)	49.6% (68/137)	6.36% [−3.80%, 16.42%]
C	20.0% (55/275)	26.3% (36/137)	−6.28% [−15.31%, 2.12%]

Note 1) RCA = right coronary artery, LAD = left anterior descending coronary artery, LCX = left circumflex coronary artery, AHA/ACC = American Heart Association/American College of Cardiology (hereinafter, the same applies unless otherwise stated)
Note 2) L = total number of target lesions (hereinafter, the same applies unless otherwise stated)

A total of 280 stents (276 BVS stents and 4 XIENCE stents) were implanted in 275 registered target lesions in the BVS group. The mean number of the implanted study device per subject was 1.1 ± 0.2; 1 device in 252 subjects and 2 devices in 14 subjects. BVS was implanted in 272 of 275 target lesions (98.9%) as scheduled. Two subjects were treated with XIENCE stent in 2 lesions because of BVS implantation failure. One subject was also treated with XIENCE stent in 1 lesion because BVS could not be used due to improper storage/maintenance. Five subjects underwent bailout procedure for 5 lesions for overlapping implantation with another BVS or XIENCE stent in addition to the BVS that had been placed as scheduled (4 lesions in 4 subjects for additional BVS and 1 lesion in 1 subject for additional XIENCE stent). A total of 138 XIENCE stents were implanted in 137 target lesions in the XIENCE group. The mean number of the implanted XIENCE stents per subject was 1.0 ± 0.2; 1 device in 130 subjects and 2 devices in 4 subjects. One subject underwent bailout procedure for 1 lesion for overlapping implantation with another XIENCE stent in addition to the stent that had been placed as planned. No subject received any device other than study device.

In both treatment groups, pre-dilatation was performed on all target lesions, approximately 35% of which required pre-dilatation more than once. Post-dilatation of the target lesions was required in 226 of 275 lesions (82.2%) in the BVS group and 106 of 137 lesions (77.4%) in the XIENCE group.

The protocol required the use of dual anti-platelet therapy (DAPT) with a thienopyridine antiplatelet agent and aspirin for at least 12 consecutive months as post-procedure anti-platelet therapy. All subjects received these 2 anti-platelet agents. At 12 months (365 days), the percentages of subjects who continued to receive the 2 antiplatelet agents were 97.0% (258 of 266 subjects) in the BVS group and 93.3% (125 of 134 subjects) in the XIENCE group, showing no significant difference between the 2 groups (Table 14). The thienopyridine antiplatelet agents used in the study were clopidogrel in 393 of 400 subjects

(98.3%) and ticlopidine in 10 of 400 subjects (2.5%). Three subjects were switched from clopidogrel to ticlopidine during follow-up. The only anti-platelet agent other than the thienopyridine antiplatelet agents and aspirin was cilostazol, which was used in 9 of 400 subjects (2.3%).

Table 14. Post-procedure antiplatelet therapy (ITT analysis)

	BVS (N = 266)	XIENCE (N = 134)	Difference between 2 groups [95% CI]
DAPT			
Subjects receiving antiplatelet therapy	100.0% (266/266)	100.0% (134/134)	0.00% [−1.42%, 2.79%]
At 30 days[1]	99.2% (264/266)	98.5% (132/134)	0.74% [−1.49%, 4.57%]
At 180 days[1]	97.7% (260/266)	94.0% (126/134)	3.71% [−0.18%, 9.22%]
At 365 days[1]	97.0% (258/266)	93.3% (125/134)	3.71% [−0.51%, 9.46%]

[1] Acceptable evaluation period is ± 7 days.
Note) The thienopyridine anti-platelet agents included clopidogrel and ticlopidine.

"TLF rate (incidence of TLF) at 12 month (393 days)," the primary endpoint, was 4.2% (11 of 265 subjects) in the BVS group and 3.8% (5 of 133 subjects) in the XIENCE group (Table 15). The difference between the 2 groups was 0.39%. The upper limit of the one-sided 95% confidence interval (CI) of the difference was 3.95%, which was less than the non-inferiority margin of 8.6%, showing the non-inferiority of BVS to XIENCE.

Table 15. Incidence of TLF at 12 months (393 days) (ITT analysis)

	BVS (N = 266)	XIENCE (N = 134)	Difference between 2 groups (upper limit of one-sided 95% CI)[1]	*P*-value for non-inferiority[2]
Primary analysis				
Incidence of TLF at 12 months	4.2% (11/265)	3.8% (5/133)	0.39% (3.95%)	<0.0001
Secondary analysis				
Incidence of TLF at 12 months	4.9% (13/265)	3.8% (5/133)	1.15% (4.75%)	0.0003

[1] The CI was determined by Farrington-Manning method.
[2] With the non-inferiority margin of 8.6%, the BVS is considered non-inferior to XIENCE stents when the one-sided non-inferiority *P*-value for Farrington-Manning test is less than the one-sided significance level of 0.05.
Note) In Study AVJ-301, MI was assessed according to 2 different definitions, i.e., the one used in the ABSORB III study (post-PCI MI, CK-MB levels > Reference value × 5; post-CABG MI, CK-MB levels > Reference value × 10) and the other one used in the SPIRIT III study (no abnormal Q wave, CK levels > Reference value × 2, and CK-MB levels > Reference value). The former definition was used for the primary analysis, while the latter was used for the secondary analysis. If the primary analysis verified the non-inferiority of the AVJ-301 group to the XIENCE group, the study was considered successful.

The submitted results of the major secondary endpoints are presented below.

Device success[ii] was observed in 271 of 274 lesions (98.9%) in the BVS group and 136 of 137 lesions (99.3%) in the XIENCE group. Procedural success[iii] was observed in 259 of 265 subjects (97.7%) in the BVS group and 132 of 134 subjects (98.5%) in the XIENCE group. Neither endpoints showed statistically significant difference between the 2 groups.

[ii] Device success was defined as implantation of the assigned device at an intended site without any device failure, successful retrieval of the delivery system, and in-device % DS of <30% as determined by core lab QCA (or visually estimated when QCA could not be performed). The use of a bailout device precluded device success. Combination with other study devices also precluded device success.
[iii] Procedural success was defined as implantation of the assigned device at an intended site without any device failure, successful retrieval of the delivery system, in-device %DS of <30% as determined by core lab QCA (or visually estimated when QCA could not be performed), and no occurrence of TLF during hospital stay (within 7 days post-procedure when hospital stay was prolonged) regardless of whether other study devices were used.

Table 16 presents the results of the clinical endpoints. The incidence of each event did not significantly differ between the BVS and XIENCE groups.

Table 16. Outcomes of clinical endpoints at 12 months (393 days) (ITT analysis)

Endpoint	BVS (N = 266) (L = 275)	XIENCE (N = 134) (L = 137)	Difference between 2 groups [95% CI]
At 12 months (393 days)			
DMR	9.8% (26/265)	8.3% (11/133)	1.54% [−5.12%, 7.05%]
TVF	6.0% (16/265)	5.3% (7/133)	0.77% [−4.91%, 5.22%]
MACE	4.2% (11/265)	3.8% (5/133)	0.39% [−4.68%, 4.18%]
TLF	4.2% (11/265)	3.8% (5/133)	0.39% [−4.68%, 4.18%]
Death/MI	4.2% (11/265)	2.3% (3/133)	1.90% [−2.65%, 5.36%]
Cardiac death/MI	3.4% (9/265)	2.3% (3/133)	1.14% [−3.32%, 4.43%]
Death	0.8% (2/265)	0.0% (0/133)	0.75% [−2.11%, 2.71%]
Cardiac death	0.0% (0/265)	0.0% (0/133)	0.00% [−2.81%, 1.43%]
MI[1]	3.4% (9/265)	2.3% (3/133)	1.14% [−3.32%, 4.43%]
TV-MI[1]	3.4% (9/265)	2.3% (3/133)	1.14% [−3.32%, 4.43%]
Coronary revascularization	7.9% (21/265)	6.8% (9/133)	1.16% [−5.05%, 6.17%]
ID-TVR[2]	4.9% (13/265)	3.8% (5/133)	1.15% [−4.00%, 5.09%]
ID-TLR[2]	2.6% (7/265)	2.3% (3/133)	0.39% [−4.00%, 3.48%]

[1] Definition in the ABSORB III study

[2] TVR was defined as re-PCI at any site of the target vessel or bypass surgery. The target vessel was defined as the entire coronary artery where the target lesion was located, including side branches (proximal and distal) and the target lesion.

Note) Subjects without DMR whose assessment was censored by each follow-up timepoint were excluded from the analysis parameter for that timepoint.

In Study AVJ-301, the incidence of the Academic Research Consortium (ARC)[20] -defined ST through 12 months (365 days) was 1.5% (4 of 262 subjects) in the BVS group and 1.5% (2 of 133 subjects) in the XIENCE group (Table 17).

Table 17. Stent thrombosis (ARC-defined definite/probable ST) through 12 months (ITT analysis)

	BVS (N = 266)	XIENCE (N = 134)	Difference between 2 groups [95% CI]
Acute ST (0-1 day)	0.0% (0/266)	0.0% (0/133)	0.00% [−2.81%, 1.42%]
Sub-acute ST (2-30 days)	1.1% (3/265)	0.8% (1/133)	0.38% [−3.09%, 2.61%]
Late ST (31-365 days)	0.4% (1/262)	0.8% (1/133)	−0.37% [−3.77%, 1.48%]
Overall ST (0-365 days)	1.5% (4/262)	1.5% (2/133)	0.02% [−3.90%, 2.60%]

Note) The events in this table were assessed for each subject.

Note) Subjects without ST whose assessment was censored by each follow-up timepoint were excluded from the analysis parameter for that timepoint.

Note) The numbers of subjects with ST classified as “definite” or “probable” according to the ARC definition are presented (hereinafter, the same applies unless otherwise stated).

Tables 18 to 20 present the results of QCA at pre-procedure, immediate post-procedure, and 13 months. At immediate post-procedure, the BVS group had a significantly lower in-device minimal lumen diameter and a significantly higher in-device % re-stenosis than the XIENCE group. At Month 13, those differences between the 2 groups were still present.

Table 18. Baseline lesion characteristics (ITT analysis)

	BVS (N = 266) (L = 275)	XIENCE (N = 134) (L = 137)	Difference [95% CI]
QCA at pre-procedure			
Lesion length (mm)	13.44 ± 5.29 (274)	13.34 ± 5.52 (137)	0.09 [−1.03, 1.21]
RVD (mm)	2.71 ± 0.45 (274)	2.79 ± 0.46 (137)	−0.08 [−0.17, 0.01]
Minimal lumen diameter (mm)	0.96 ± 0.33 (274)	0.99 ± 0.36 (137)	−0.03 [−0.10, 0.04]
% Diameter stenosis	64.53 ± 11.14 (274)	64.66 ± 10.90 (137)	−0.13 [−2.39, 2.13]

Table 19. Target lesion assessment at immediate post-procedure (ITT analysis)

	BVS (N = 266) (L = 275)	XIENCE (N = 134) (L = 137)	Difference between 2 groups [95% CI][1]
QCA at immediate post-procedure			
RVD (mm) at immediate post-procedure	2.75 ± 0.42 (275)	2.85 ± 0.43 (137)	−0.10 [−0.19, −0.01]
In-segment minimal lumen diameter (mm) at immediate post-procedure	2.20 ± 0.39 (275)	2.27 ± 0.43 (137)	−0.06 [−0.15, 0.02]
In-device minimal lumen diameter (mm) at immediate post-procedure	2.43 ± 0.37 (275)	2.64 ± 0.40 (137)	−0.21 [−0.29, −0.13]
In-segment diameter stenosis (%) at immediate post-procedure	19.97 ± 6.67 (275)	20.57 ± 8.80 (137)	−0.59 [−2.27, 1.09]
In-device diameter stenosis (%) at immediate post-procedure	11.59 ± 7.54 (275)	7.25 ± 8.11 (137)	4.34 [2.70, 5.97]
In-segment acute gain (mm)	1.25 ± 0.41 (274)	1.28 ± 0.45 (137)	−0.03 [−0.12, 0.06]
In-device acute gain (mm)	1.47 ± 0.40 (274)	1.65 ± 0.40 (137)	−0.18 [−0.26, −0.10]

Table 20. Results of QCA at 13-month follow-up (FAS analysis)

	BVS (N = 252) (L = 260)	XIENCE (N = 126) (L = 129)	Difference [95% CI]
QCA at 13 months			
RVD (mm)	2.70 ± 0.42 (260)	2.80 ± 0.44 (129)	−0.09 [−0.19, −0.00]
In-segment minimal lumen diameter (mm)	2.08 ± 0.45 (260)	2.15 ± 0.50 (129)	−0.07 [−0.17, 0.03]
In-device minimal lumen diameter (mm)	2.23 ± 0.47 (260)	2.48 ± 0.53 (129)	−0.25 [−0.35, −0.14]
In-segment % diameter stenosis	23.44 ± 11.31 (260)	23.65 ± 12.25 (129)	−0.21 [−2.74, 2.33]
In-device % diameter stenosis	17.38 ± 12.83 (260)	11.72 ± 12.31 (128)	5.66 [3.00, 8.31]
In-segment late loss (mm)	0.13 ± 0.30 (260)	0.12 ± 0.32 (129)	0.01 [−0.06, 0.08]
In-device late loss (mm)	0.19 ± 0.31 (260)	0.16 ± 0.33 (129)	0.03 [−0.04, 0.10]
In-segment % re-stenosis	1.9% (5/260)	3.9% (5/129)	−1.95% [−6.95%, 1.38%]
In-device % re-stenosis	1.5% (4/260)	1.6% (2/128)	−0.02% [−4.09%, 2.58%]

Figure 8 presents the in-segment late loss (LL) at 13 months. The in-segment LL at 13 months was 0.13 ± 0.30 mm in the BVS group and 0.12 ± 0.32 mm in the XIENCE group, indicating the non-inferiority of BVS to XIENCE stents in terms of the occurrence of in-segment LL (non-inferiority *P*-value < 0.0001).

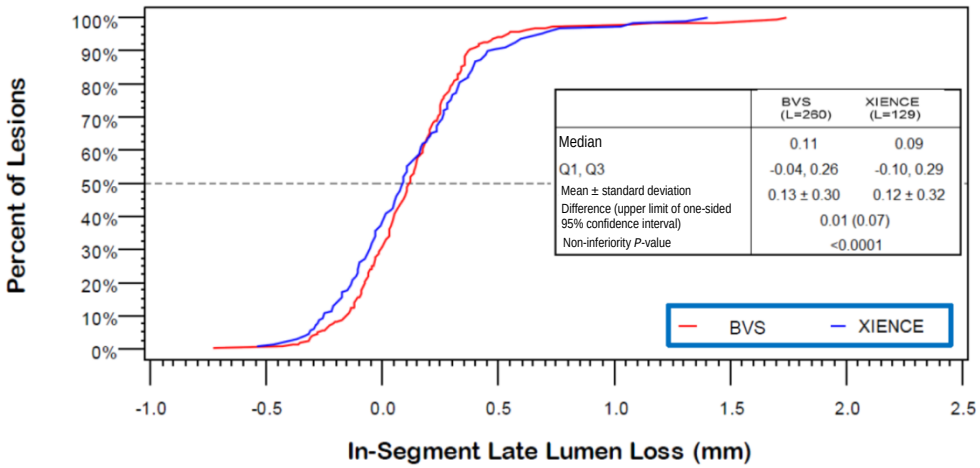


Figure 8. Cumulative distribution curve of in-segment late loss at 13 months

The non-inferiority *P*-value was calculated using asymptotic test using the non-inferiority limit of 0.195 mm. The significance level of 0.05 was used.

A total of 147 subjects were included in the MSCT subgroup, and 84 subjects (88 lesions) in the BVS group and 42 subjects (42 lesions) in the XIENCE group underwent MSCT at 13 months. These subjects were included in the full analysis set (FAS) for MSCT at 13 months. One subject in the BVS group received treatment with a DES in the target lesion for intervention of ST. A total of 83 subjects (87 lesions) were treated with BVS only. Stenosis assessment was possible in 82 of 88 lesions (93.2%) in the BVS group and 28 of 42 lesions (66.7%) in the XIENCE group, being significantly higher in the BVS group than that in the XIENCE group (Table 21). No significant stenosis was observed in either group. One of the lesions that was not evaluable in the BVS group could not be assessed for stenosis because of the artifact of a metal stent implanted for ST intervention. When the lesions implanted with BVS only were analyzed, 82 of 87 lesions (94.3%) were evaluable for stenosis by MSCT.

Table 21. Assessment of significant stenosis by MSCT (FAS analysis)

	BVS (N = 84) (L = 88)	**XIENCE (N = 42) (L = 42)**	**Difference [95% CI]**
Evaluable for stenosis	93.2% (82/88)	66.7% (28/42)	26.52% [12.21%, 42.07%]
- Significant stenosis	0.0% (0/88)	0.0% (0/42)	0.00% [−8.38%, 4.18%]
- No significant stenosis	93.2% (82/88)	66.7% (28/42)	26.52% [12.21%, 42.07%]
Not evaluable for stenosis	6.8% (6/88)	33.3% (14/42)	−26.52% [−42.07%, −12.21%]

A total of 828 adverse events (572 in the BVS group, 256 in the XIENCE group) in 296 subjects (197 in the BVS group, 99 in the XIENCE group) were reported by study sites within 393 days post-procedure. A total of 122 adverse events (86 in the BVS group, 36 in the XIENCE group) in 89 subjects (59 in the BVS group, 30 in the XIENCE group) were serious. Table 22 presents serious adverse events that ≥2 events occurred in the BVS group.

Table 22. Serious adverse events reported by study sites within 393 days post-procedure

System Organ Class Preferred Term	BVS (N = 266)	XIENCE (N = 134)	Total (N = 400)
Cardiac disorders	10.5% (28/266)	9.0% (12/134)	10.0% (40/400)
Angina pectoris	2.6% (7/266)	3.0% (4/134)	2.8% (11/400)
Myocardial infarction	1.9% (5/266)	1.5% (2/134)	1.8% (7/400)
Myocardial ischaemia	1.9% (5/266)	0.0% (0/134)	1.3% (5/400)
Coronary artery stenosis	1.1% (3/266)	0.7% (1/134)	1.0% (4/400)
Coronary artery disease	0.8% (2/266)	0.7% (1/134)	0.8% (3/400)
Ear and labyrinth disorders	0.8% (2/266)	0.0% (0/134)	0.5% (2/400)
Eye disorders	1.5% (4/266)	0.7% (1/134)	1.3% (5/400)
Cataract	0.8% (2/266)	0.0% (0/134)	0.5% (2/400)
Gastrointestinal disorders	1.9% (5/266)	1.5% (2/134)	1.8% (7/400)
Inguinal hernia	0.8% (2/266)	0.7% (1/134)	0.8% (3/400)
General disorders and administration site conditions	1.9% (5/266)	0.7% (1/134)	1.5% (6/400)
Device related thrombosis	1.5% (4/266)	0.7% (1/134)	1.3% (5/400)
Infections and infestations	2.3% (6/266)	0.7% (1/134)	1.8% (7/400)
Herpes zoster	0.8% (2/266)	0.0% (0/134)	0.5% (2/400)
Injury, poisoning and procedural complications	2.6% (7/266)	5.2% (7/134)	3.5% (14/400)
Coronary artery restenosis	0.8% (2/266)	2.2% (3/134)	1.3% (5/400)
Investigations	0.8% (2/266)	0.7% (1/134)	0.8% (3/400)
Metabolism and nutrition disorders	0.8% (2/266)	0.0% (0/134)	0.5% (2/400)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1.9% (5/266)	3.0% (4/134)	2.3% (9/400)
Nervous system disorders	2.6% (7/266)	0.7% (1/134)	2.0% (8/400)
Cerebral infarction	1.1% (3/266)	0.0% (0/134)	0.8% (3/400)
Renal and urinary disorders	0.8% (2/266)	0.0% (0/134)	0.5% (2/400)
Vascular disorders	1.9% (5/266)	2.2% (3/134)	2.0% (8/400)
Peripheral arterial occlusive disease	0.8% (2/266)	0.7% (1/134)	0.8% (3/400)
Total	22.2% (59/266)	22.4% (30/134)	22.3% (89/400)

A total of 52 product malfunctions were reported in 37 subjects within 393 days post-procedure (Table 23); 41 malfunctions in 32 subjects in the BVS group and 11 malfunctions in 5 subjects in the XIENCE group. The most common malfunction was difficulty in pass-through where a post-dilatation balloon catheter or catheter for intravascular diagnostic imaging could not pass through the implanted scaffold or stent; 21 events in 21 subjects in the BVS group and 5 events in 2 subjects in the XIENCE group. One event in 1 subject in the BVS group was difficulty in pass-through associated with XIENCE PRIME that was placed because of BVS implantation failure. There were 11 events of failure to pass through lesion in 8 subjects in the BVS group and 1 event in 1 subject in the XIENCE group. Despite multiple attempts to deliver BVS to the target lesion, the device failed to pass through the lesion in 2 subjects, resulting in implantation of XIENCE stent. No subject received other stents because of failure to place XIENCE stent.

Table 23. Occurrence of product malfunctions

Product malfunction	BVS			XIENCE		
	No. of subjects (N = 266)	No. of devices (S = 280)	No. of malfunctions	No. of subjects (N = 134)	No. of devices (S = 138)	No. of malfunctions
Difficulty in pass-through	21[*1]	21[*1]	21[*1]	2	2	5
Failure to pass through lesion	8	11	11	1	1	1
Physical resistance	4	4	4	1	1	1
Difficulty in placement	3	3	3	0	0	0
Improper use of device	1	1	1	1	1	1
Difficulty in retrieval	0	0	0	1	1	1
Stent deformity/damage	0	0	0	1	1	1
Device breakage	0	0	0	1	1	1
Change in scaffold's shape or gap	1	1	1	0	0	0
Total	32[*2]	39[*1,3]	41	5[*2]	5[*3]	11

[*1] Including 1 event of difficulty in pass-through associated with XIENCE PRIME that was placed because of AVJ-301 implantation failure in 1 subject in the BVS group.
[*2] Subjects were counted only once even when they experienced more than one malfunction.
[*3] Devices were counted only once even when they caused more than one malfunction.
Note) S = number of devices.
Note) Definition of product malfunction
Difficulty in pass-through: In this section, it is defined as a post-dilatation balloon, intravascular diagnostic imaging device, etc. not re-passing or being difficult to re-pass, or not passing through the placed scaffold or stent. In the clinical study report, it was reported as "Difficulty in positioning."
Failure to pass through lesion: The investigational device does not reach the intended position (lesion).
Physical resistance: Resistance is felt when the investigational device is rotated or torque is applied to the investigational device, or placement of other devices, such as a guide wire, interferes with the delivery of the investigational device.
Difficulty in placement: It is impossible or difficult to place the device at the intended position.

6.A.(2) ABSORB III study (study period, [redacted] 20[redacted] to [redacted] 20[redacted] [planned])

The ABSORB III study is a prospective, randomized, active-controlled, single-blind, global, multicenter, clinical study conducted as Investigational Device Exemption (IDE) study to obtain US Premarket Approval (PMA). This study was intended to evaluate the efficacy and safety of AVJ-301 versus commercial DESs in the treatment of patients with ischemic heart disease caused by ≤2 *de novo* native coronary artery lesions in separate vessels. XIENCE V, XIENCE PRIME, and XIENCE Xpedition, which are commercial DESs, was used as control devices. The study was conducted in 2008 patients (1322 in the BVS group, 686 in the XIENCE group) at 193 study sites (191 in the US, 2 in Australia). The lesion characteristics were as follows: target lesion length, 12.60 ± 5.41 mm in the BVS group and 13.12 ± 5.82 mm in the XIENCE group; ACC/AHA type B2/C lesion, 68.7% (949 of 1381 lesions) in the BVS group and 72.5% (513 of 708 lesions) in the XIENCE group.

The ABSORB III study included patients who had a target lesion in a native coronary artery, % DS of ≥50% and <100% as visually estimated or quantitatively determined, a blood flow of TIMI grade ≥1, % stenosis of ≥70%, and ischemic finding as revealed by function test (e.g., fractional flow reserve [FFR] and excise stress test), unstable angina, or postinfarction angina. Target lesions were defined as 1 or 2 *de novo* lesions located in separate coronary arteries with an RVD of ≥2.5 and ≤3.75 mm and a length of ≤24 mm as visually estimated. This study excluded lesions in which pre-dilatation or delivery was difficult, lesions in the left major artery, aorta-ostial lesions, bifurcation lesions, and thrombotic lesions. Subjects underwent follow-up at pre-procedure and immediate post-procedure, during hospitalization, and at 1 and 6 months and 1, 2, 3, 4, and 5 years post-procedure.

The primary endpoint of this study was the TLF rate (i.e., incidence of TLF) at 12 months post-procedure, defined as the composite of cardiac death, TV-MI, and ID-TLR.

The secondary endpoints were acute success (device success assessed for each lesion and procedural success assessed for each subject), clinical endpoints (death [cardiac death, vascular death, and non-cardiac death], MI [QMI and NQMI], TLR, TVR, and all coronary revascularization, as single and composite endpoint), and ST during hospitalization, and at 1, 6 and 12 months, and 2, 3, 4, and 5 years post-procedure.

Incidence of TLFs at 12 months post-procedure, the primary endpoint, was analyzed in the ITT population. The results were 7.8% (102 of 1313 subjects) in the BVS group and 6.1% (41 of 677 subjects) in the XIENCE group. The difference between the 2 groups was 1.71%. The upper limit of the 97.5% CI of the difference was 3.93%, which was lower than the non-inferiority margin of 4.5%, showing the non-inferiority of BVS to XIENCE stents (non-inferiority *P*-value = 0.0070) (Table 24).

Table 24. Results of non-inferiority test of primary endpoint (ITT analysis)

	BVS (N = 1322)	XIENCE (N = 686)	Difference (upper limit of one-sided 97.5% CL[1])	Non-inferiority *P*-value[2]
1-Year TLF	7.8% (102/1313)	6.1% (41/677)	1.71% (3.93%)	0.0070

1 Upper limit of one-sided 97.5% CI determined by Farrington-Manning method
2 One-sided *P*-value for Farrington-Manning test with the non-inferiority margin of 4.5%. The significance level *P* was 0.0025.

Table 25 presents the results of the secondary endpoints subjected to superiority test. The 3 protocol-defined endpoints were subjected to superiority test, showing no significant difference between the 2 groups. Superiority of BVS to XIENCE stents could not be demonstrated.

Table 25. Results of superiority test of secondary endpoints (ITT analysis)

	BVS (N = 1322)	XIENCE (N = 686)	Difference [95% CL][2]	*P*-value[3]
1-Year angina pectoris[1]	18.3% (238/1303)	18.4% (125/678)	−0.17% [−3.77%, 3.42%]	0.9256
1-Year all revascularization	9.1% (120/1313)	8.1% (55/677)	1.02% [−1.57%, 3.60%]	0.5040
1-Year ID-TVR	5.0% (66/1313)	3.7% (25/677)	1.33% [−0.51%, 3.18%]	0.2126

1 Only events that occurred at ≥7 days post-procedure
2 The two-sided 95% CI as determined by Pearson's χ^2 test for angina, and by exact test for all revascularization and ID-TVR
3 Pearson's χ^2 test for angina, and Fisher's exact test for all revascularization and ID-TVR. The significance level *P* was 0.05 (superiority test).

Table 26 presents the clinical results at 1 year. The composite endpoint or single endpoints showed no significant difference between the 2 groups.

Table 26. Outcomes of clinical endpoints at 12 months (393 days) (ITT analysis)

	BVS (N = 1322)	XIENCE (N = 686)	Difference [95% CI]
DMR	14.0% (184/1313)	11.5% (78/677)	2.49% [−0.68%, 5.45%]
TVF	10.0% (131/1313)	7.8% (53/677)	2.15% [−0.58%, 4.65%]
TLF	7.8% (102/1313)	6.1% (41/677)	1.71% [−0.74%, 3.93%]
Cardiac death/all MI	7.5% (98/1313)	5.8% (39/677)	1.70% [−0.70%, 3.87%]
All death	1.1% (15/1313)	0.4% (3/677)	0.70% [−0.26%, 1.49%]
- Cardiac death	0.6% (8/1313)	0.1% (1/677)	0.46% [−0.29%, 1.06%]
All MI	6.9% (90/1313)	5.6% (38/677)	1.24% [−1.11%, 3.36%]
- TV-MI	6.0% (79/1313)	4.6% (31/677)	1.44% [−0.74%, 3.39%]
- TV-QMI	0.7% (9/1313)	0.3% (2/677)	0.39% [−0.45%, 1.04%]
- TV-NQMI	5.3% (70/1313)	4.3% (29/677)	1.05% [−1.06%, 2.91%]
All revascularization	9.1% (120/1313)	8.1% (55/677)	1.02% [−1.70%, 3.50%]
- All TVR	5.1% (67/1313)	3.8% (26/677)	1.26% [−0.77%, 3.06%]
- ID-TVR	5.0% (66/1313)	3.7% (25/677)	1.33% [−0.67%, 3.10%]
- All TLR	3.2% (42/1313)	2.7% (18/677)	0.54% [−1.18%, 2.00%]
- ID-TLR	3.0% (40/1313)	2.5% (17/677)	0.54% [−1.14%, 1.96%]

Table 27 presents the incidence of ST. The cumulative incidence of ST through 1 year was 1.54% (20 of 1301 subjects) in the BVS group and 0.74% (5 of 675 subjects) in the XIENCE group. One subject in the BVS group received XIENCE stent.

Table 27. ST through 12 months (ITT analysis)

	BVS (N = 1322)	XIENCE (N = 686)	Difference between 2 groups [95% CI][1]
Acute ST (0-1 day)	0.15% (2/1320)	0.58% (4/686)	−0.43% [−1.34%, 0.10%]
Sub-acute ST (2-30 days)	0.91% (12/1315)	0.15% (1/686)	0.77% [−0.01%, 1.45%]
Late ST (31-365 days)	0.46% (6/1299)	0.00% (0/675)	0.46% [−0.16%, 1.00%]
Overall ST (0-365 days)	1.54% (20/1301)	0.74% (5/675)	0.80% [−0.32%, 1.72%]

6.A.(3) ABSORB III pharmacokinetics sub-study (study period, [redacted] 20[redacted] to [redacted] 20[redacted] [planned])

As part of the ABSORB III study, a PK sub-study was conducted in 12 subjects, who were not included in the analyses of the ABSORB III study. This sub-study evaluated the PK of everolimus eluting from implanted BVS in 12 subjects who received treatment with AVJ-301 only in ≤2 *de novo* native coronary artery lesions.

Blood samples were collected at baseline (before the procedure), 10 and 30 minutes, 1, 2, 4, 6, 12, 24 (1 day), 48 (2 days), 72 (3 days), 96 (4 days), 120 (5 days), 168 (7 days), 336 (14 days), and 720 (30 days) hours post-procedure.

The dose of everolimus per subject ranged from 181 to 443 µg. The maximum concentration of everolimus in blood ranged from 1.085 to 4.460 ng/mL, which was reached between 0.17 and 2.37 hours (actual time) post-procedure. The blood concentration of everolimus was proportional to its dose. The elimination half-life ranged from 45.9 to 115 hours. Everolimus was detected in blood up to 7 days. AUC_{24h} was 12.09 to 44.22 ng•h/mL, with AUC_{last} of 25.37 to 104.6 ng•h/mL and $AUC_{0-\infty}$ of 33.15 to 120.8 ng•h/mL.

To enable everolimus to exert the systemic effect (immunosuppression after organ transplant), its blood trough concentration needs to be chronically maintained at ≥3.0 ng/mL. The blood everolimus

concentration after BVS implantation was below this concentration and rapidly decreased, suggesting limited systemic effects of everolimus eluting from BVS.

6.A.(4) Summary of the results of other clinical studies

6.A.(4).1) ABSORB Cohort A (study period, March 2006 to August 2011)

An exploratory clinical study was conducted to evaluate the performance and feasibility of BVS-A in the treatment of patients with a single *de novo* native coronary artery lesion. A total of 30 patients were enrolled in the study at 4 study sites (the Netherlands, Poland, Denmark, and New Zealand) from March 7, 2006 to July 18, 2006 (target lesion length, 8.93 ± 3.58 mm; ACC/AHA type B2/C, 40% [12 of 30 lesions]). Of the 30 subjects, 4 underwent bailout procedures.

Table 28 presents the clinical outcomes through 5 years.

Table 28. Clinical outcomes through 5 years (ITT analysis)

	6 months (N = 30)	12 months (N = 29)	2 years (N = 29)	3 years (N = 29)	4 years (N = 29)	5 years (N = 29)
TVF	3.3% (1)	3.4% (1)	3.4% (1)	3.4% (1)	3.4% (1)	6.9% (2)
MACE	3.3% (1)	3.4% (1)	3.4% (1)	3.4% (1)	3.4% (1)	3.4% (1)
Cardiac death	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
MI	3.3% (1)	3.4% (1)	3.4% (1)	3.4% (1)	3.4% (1)	3.4% (1)
QMI	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
NQMI	3.3% (1)	3.4% (1)	3.4% (1)	3.4% (1)	3.4% (1)	3.4% (1)
ID-TLR	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
ID-TVR	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	3.4% (1)
ST	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)

6.A.(4).2) ABSORB Cohort B (study period, March 2009 to [redacted] 20[redacted])

An exploratory clinical study was conducted as an extension study of ABSORB Cohort A (the first clinical study of BVS), to evaluate the performance and feasibility of BVS-B in the treatment of patients with a single *de novo* native coronary artery lesion.

In this prospective, non-randomized, single-arm, open-label, global, multicenter study, 101 patients were enrolled at 12 study sites (target lesion length, 9.92 ± 3.65 mm; ACC/AHA type B2/C, 44% [44 of 100 lesions]).

Table 29 presents the clinical outcomes through 5 years.

Table 29. Clinical outcomes through 5 years (ITT analysis)

	6 months (N = 101)	12 months (N = 101)	18 months (N = 101)	2 years (N = 100)	3 years (N = 100)	4 years (N = 100)	5 years (N = 100)
TVF	5.0% (5)	6.9% (7)	10.9% (11)	11.0% (11)	13.0% (13)	13.1% (13)	14.0% (14)
MACE	5.0% (5)	6.9% (7)	7.9% (8)	9.0% (9)	10.0% (10)	10.0% (10)	11.0% (11)
Cardiac death	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
MI	3.0% (3)	3.0% (3)	3.0% (3)	3.0% (3)	3.0% (3)	3.0% (3)	3.0% (3)
QMI	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
NQMI	3.0% (3)	3.0% (3)	3.0% (3)	3.0% (3)	3.0% (3)	3.0% (3)	3.0% (3)
ID-TLR	2.0% (2)	4.0% (4)	5.0% (5)	6.0% (6)	7.0% (7)	7.0% (7)	8.0% (8)
ID-TVR	2.0% (2)	4.0% (4)	7.9% (8)	8.0% (8)	10.0% (10)	10.0% (10)	11.0% (11)
ST	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)

6.A.(4).3) ABSORB EXTEND study (study period, [redacted] 20[redacted] to [redacted] 20[redacted] [planned])

The ABSORB EXTEND study is an extension study for ABSORB Cohorts A and B (the first clinical study of BVS) conducted in patients with ≤2 *de novo* native coronary artery lesions (2 lesions in separate coronary arteries) with the intention to treat a broader patient population, including subjects with longer lesions. The study was started with BVS-B, but the device was switched to AVJ-301 during the registration process.

In this prospective, non-randomized, single-arm, open-label, global, multicenter study, 812 patients were enrolled at 56 study sites, including those in Japan (target lesion length, 12.33 ± 5.26 mm; ACC/AHA type B2/C, 44.7% [386 of 864 lesions]).

Table 30 presents the clinical outcomes through 1 year.

Table 30. Results of ABSORB EXTEND study (ITT analysis)

Overall EXTEND population	1 month (N = 812)	6 months (N = 812)	1 year (N = 812)
TVF	2.6% (21/812)	3.7% (30/812)	5.5% (45/812)
MACE	2.6% (21/812)	3.4% (28/812)	5.0% (41/812)
TLF	2.6% (21/812)	3.4% (28/812)	5.0% (41/812)
Cardiac death	0.2% (2/812)	0.5% (4/812)	0.7% (6/812))
MI	2.5% (20/812)	3.0% (24/812)	3.3% (27/812)
- TV MI	2.5% (20/812)	3.0% (24/812)	3.3% (27/812)
- TV-QMI	0.7% (6/812)	0.9% (7/812)	1.0% (8/812)
- TV-NQMI	1.7% (14/812)	2.1% (17/812)	2.3% (19/812)
ID-TLR	0.5% (4/812)	1.1% (9/812)	2.3% (19/812)
ID-TVR	0.5% (4/812)	1.4% (11/812)	2.8% (23/812)
ST	0.6% (5/812)	0.9% (7/809)	1.0% (8/809)
Japanese subjects	**1 month (N = 40)**	**6 months (N = 40)**	**1 year (N = 40)**
TVF	2.5% (1)	2.5% (1)	5.0% (2)
MACE	2.5% (1)	2.5% (1)	5.0% (2)
TLF	2.5% (1)	2.5% (1)	5.0% (2)
Cardiac death	0.0% (0)	0.0% (0)	2.5% (1)
MI	2.5% (1)	2.5% (1)	2.5% (1)
- TV MI	2.5% (1)	2.5% (1)	2.5% (1)
- TV-QMI	0.0% (0)	0.0% (0)	0.0% (0)
- TV-NQMI	2.5% (1)	2.5% (1)	2.5% (1)
ID-TLR	0.0% (0)	0.0% (0)	0.0% (0)
ID-TVR	0.0% (0)	0.0% (0)	0.0% (0)
ST	0.0% (0)	0.0% (0)	0.0% (0)

6.A.(4).4) ABSORB II study (study period, November 2011 to July 2018 [planned])

The ABSORB II study is a post-marketing clinical study to evaluate BVS in comparison with XIENCE PRIME, a commercial DES. As in the ABSORB EXTEND study, this study was started with BVS-B, but the device was switched to AVJ-301 during the registration process.

In this prospective, randomized (2:1 for BVS versus XIENCE), active-controlled, single-blind, global (Europe and New Zealand), multicenter study, 501 patients (335 in the BVS group, 166 in the XIENCE group) were enrolled at 46 study sites (target lesion length, 13.81 ± 6.52 mm; ACC/AHA type B2/C, 45.5% [165 of 363 lesions] for the BVS group).

Table 31 presents the clinical outcomes through 1 year. Table 32 presents the incidence of ST.

Table 31. Results of the ABSORB II study at 1 year (ITT analysis)

	BVS (N = 335)	XIENCE (N = 166)	Difference [95% CI]
DMR	7.3% (24/331)	9.1% (15/165)	−1.84% [−7.69%, 2.98%]
TVF	5.4% (18/331)	4.8% (8/165)	0.59% [−4.26%, 4.41%]
TLF	4.8% (16/331)	3.0% (5/165)	1.80% [−2.48%, 5.16%]
Cardiac death/all MI	4.5% (15/331)	1.2% (2/165)	3.32% [−0.25%, 6.26%]
All death	0.0% (0/331)	0.6% (1/165)	−0.61% [−3.35%, 0.65%]
-Cardiac death	0.0% (0/331)	0.0% (0/165)	0.00% [NA]
All MI	4.5% (15/331)	1.2% (2/165)	3.32% [−0.25%, 6.26%]
- TV-MI	4.2% (14/331)	1.2% (2/165)	3.02% [−0.51%, 5.90]
- TV-QMI	0.6% (2/331)	0.0% (0/165)	0.60% [−1.71%, 2.18%]
- TV-NQMI	3.6% (12/331)	1.2% (2/165)	2.41% [−1.05%, 5.16%]
All revascularization	3.6% (12/331)	7.3% (12/165)	−3.65% [−8.89%, 0.37%]
-All TVR	2.4% (8/331)	4.8% (8/165)	−2.43% [−7.01%, 0.86%]
- ID-TVR	1.8% (6/331)	3.6% (6/165)	−1.82% [−6.01%, 1.04%]
-All TLR	1.2% (4/331)	1.8% (3/165)	−0.61% [−4.08%, 1.60%]
- ID-TLR	1.2% (4/331)	1.8% (3/165)	−0.61% [−4.08%, 1.60%]

Table 32. ST through 12 months (ITT analysis)

	BVS (N = 335)	XIENCE (N = 166)	Difference between 2 groups [95% CI]
ST	0.9% (3/329)	0.0% (0/164)	0.91% [−1.45%, 2.65%]

6.A.(4).5) ABSORB China study (study period, [redacted] 20[redacted] to [redacted] 20[redacted] [planned])

The ABSORB China study is a randomized, confirmatory clinical study conducted to evaluate the safety and efficacy of AVJ-301 versus XIENCE V in the treatment of Chinese patients with a *de novo* native coronary artery lesion, with the intention to obtain approval in China.

In this prospective, randomized (1:1 for BVS versus XIENCE), active-controlled, open-label, multicenter study, 480 patients (241 in the AVJ-301 group, 239 in the XIENCE group) were enrolled at 24 study sites (target lesion length, 14.16 ± 4.99 mm; ACC/AHA type B2/C, 75.8% [182 of 240 lesions] for the BVS group).

The primary endpoint of this study was in-segment LL at 1 year. Table 33 presents the results of the primary endpoint. Table 34 presents the results of the major secondary clinical endpoints through 1 year. Table 35 presents the incidence of ST.

Table 33. Primary endpoint analysis of the ABSORB China study (PTE population)

	BVS (N = 228)	XIENCE (N = 232)	Difference (upper limit of one-sided 97.5% CI)	Non-inferior *P*-value
In-segment LL (mm) at 1 year	0.19 ± 0.38	0.13 ± 0.38	0.061	0.0099
Mean ± SD (*n*)	(200)	(195)	(0.136)	

Note) The analysis of the primary endpoint was performed on a subject-by-subject base.
For subjects with multiple target lesions treated, the mean in-segment LL was used in the analysis.

Table 34. Major secondary clinical endpoints of the ABSORB China study at 1 year (PTE population)

	BVS (N = 228)	XIENCE (N = 232)	Difference [95% CI]
DMR	7.5% (17/228)	9.5% (22/232)	−2.03% [−7.26%, 3.18%]
TVF	3.5% (8/228)	5.6% (13/232)	−2.09% [−6.22%, 1.90%]
TLF	3.1% (7/228)	3.9% (9/232)	−0.81% [−4.49%, 2.81%]
Cardiac death/all MI	1.3% (3/228)	1.7% (4/232)	−0.41% [−3.17%, 2.29%]
All death	0.0% (0/228)	1.7% (4/232)	−1.72% [−4.35%, 0.24%]
- Cardiac death	0.0% (0/228)	0.9% (2/232)	−0.86% [−3.09%, 0.91%]
All MI	1.3% (3/228)	1.7% (4/232)	−0.41% [−3.17%, 2.29%]
- TV-MI	1.3% (3/228)	0.9% (2/232)	0.45% [−1.94%, 3.01%]
- TV-QMI	0.9% (2/228)	0.0% (0/232)	0.88% [−0.87%, 3.14%]
- TV-NQMI	0.4% (1/228)	0.9% (2/232)	−0.42% [-2.68%, 1.68%]
All revascularization	7.0% (16/228)	7.3% (17/232)	−0.31% [−5.19%, 4.58%]
-All TVR	3.9% (9/228)	5.2% (12/232)	−1.23% [−5.32%, 2.80%]
- ID-TVR	3.1% (7/228)	3.9% (9/232)	−0.81% [−4.49%, 2.81%]
-All TLR	3.1% (7/228)	3.0% (7/232)	0.05% [−3.41%, 3.55%]
- ID-TLR	2.6% (6/228)	2.2% (5/232)	0.48% [−2.65%, 3.71%]

Table 35. ST through 12 months (PTE population)

	BVS (N = 228)	XIENCE (N = 232)	Difference between 2 groups [95% CI]
ST	0.4% (1/228)	0.0% (0/228)	0.44% [−1.26%, 2.44%]

6.B. Outline of the review conducted by PMDA

PMDA's reviews focused on the following issues:

1. Efficacy and safety of Absorb GT1 BVS
   (1) Efficacy and safety of Absorb GT1 BVS through 1 year
      1) Thrombosis
      2) Myocardial infarction
      3) Procedural problems identified in Study AVJ-301
   (2) Efficacy and safety of Absorb GT1 BVS at ≥1 year
      1) Long-term outcomes of each study
      2) Thrombosis
   (3) Safety of additional interventions
2. Antiplatelet therapy
3. Post-marketing safety measures
4. Risk-benefit balance

6.B.1. Efficacy and safety of Absorb GT1 BVS

In recent clinical studies of DESs, TLF at 12 months is commonly used as the primary endpoint. Absorb GT1 BVS has the same clinical positioning as DESs. The clinical studies of Absorb GT1 BVS were designed to employ the same follow-up timepoints and endpoints as those for DESs. Unlike DESs, however, Absorb GT1 BVS has the novel characteristics; it degrades and resorbs over time. The efficacy and safety of resorbed Absorb GT1 BVS should therefore be verified. The results of clinical studies of Absorb GT1 BVS were reviewed to evaluate its efficacy and safety (1) through 1 year and (2) at ≥1 year, as well as to assess (3) the safety of additional interventions.

6.B.1.(1) Efficacy and safety of Absorb GT1 BVS through 1 year

Study AVJ-301 and the ABSORB III study were the first large-scale clinical studies that evaluated Absorb GT1 BVS. Both studies successfully demonstrated the non-inferiority of AVJ-301 to XIENCE stents, which have been marketed for a long period of time, in terms of TLF at 1 year as the primary endpoint.

However, the incidence of ST and MI through 1 year tended to be higher in the AVJ-301 group than in the XIENCE group, although the difference was not significant. In addition, some procedural problems with Absorb GT1 BVS were reported in the Japanese clinical study. The applicant explained that the safety of Absorb GT1 BVS was assured as described in Sections 6.B.1.(1).1) to 6.B.1.(1).3) below.

6.B.1.(1).1) Thrombosis

The ABSORB III study showed that the BVS group tended to have a higher point estimate of the incidence of ST through 1 year (1.54%) than that of the XIENCE group (0.74%). BVS has struts with a thickness of 157 μm, which is 81 μm thicker than the struts of XIENCE stent. Thick struts may be a disadvantage in achieving a sufficient lumen diameter especially in small blood vessels. The protocol of the ABSORB III study required a visually estimated RVD of ≥2.5 and ≤3.75 mm as an inclusion criterion. In general, however, visual estimation overestimates lesions by approximately 0.25 mm compared with QCA. With the measurement of 2.25 mm by QCA as the threshold, the incidence of ST through 1 year was analyzed separately for subjects having an RVD of <2.25 mm and those having an RVD of ≥2.25 mm.

Table 36 presents the results of the subgroup analysis. In the RVD ≥2.25 mm subgroup, the incidence of ST was 0.85% in the BVS group, comparable to that in the XIENCE group (0.56%) ($P = 0.76$). In the ABSORB III study, an RVD of <2.25 mm versus ≥2.25 mm ($P = 0.0002$) and overall diabetes mellitus ($P = 0.0018$) were identified as predictive factors of ST. The treatment group (BVS versus XIENCE) was not a significant predictive factor ($P = 0.1210$) (Table 37). A small vessel size[21] and diabetes mellitus[22] have also been reported as predictive factors with conventional DESs, and are not specific to BVS.

Table 36. Clinical results through 1 year by pre-procedure RVD (ABSORB III study) (ITT analysis)

Endpoint	Pre-procedure RVD ≥2.25 mm Median = 2.74 mm		Pre-procedure RVD <2.25 mm Median = 2.09 mm	
	BVS (N = 1074)	XIENCE (N = 549)	BVS (N = 242)	XIENCE (N = 133)
TLF	6.7% (71/1067)	5.5% (30/542)	12.9% (31/241)	8.3% (11/133)
Cardiac death	0.6% (6/1067)	0.2% (1/542)	0.8% (2/241)	0.0% (0/133)
TV-MI	5.2% (55/1067)	4.6% (25/542)	10.0% (24/241)	4.5% (6/133)
ID-TLR	2.2% (24/1067)	1.5% (8/542)	6.6% (16/241)	6.8% (9/133)
ST	0.85% (9/1058)	0.56% (3/540)	4.62% (11/238)	1.50% (2/133)

Table 37. Predictive factors of ST through 1 year by multivariate logistic analysis (ABSORB III study)

Variable	Comparison	Coefficient (standard error)[1]	*P*-value[2]	Relative risk [95% CI]
Treatment group	BVS versus XIENCE	−0.78 (0.51)	0.1210	2.16 [0.82, 5.68]
Overall diabetes mellitus	Diabetes mellitus versus non-diabetes mellitus	1.32 (0.42)	0.0018	3.66 [1.63, 8.21]
Pre-procedure RVD	<2.25 mm versus ≥2.25 mm	1.53 (0.41)	0.0002	4.48 [2.07, 9.70]

[1] The coefficients and standard errors were based on the final model.
[2] The *P* values were determined by Wald's χ^2 test in the final model. A multivariate logistic model was based on backward elimination. Pearson Goodness-of fit *P*-value = 0.2715.

Table 38 presents the incidence of ST and TLF by vessel diameter in Study AVJ-301.

Table 38. Clinical outcomes through 1 year by pre-procedure RVD (Study AVJ-301) (ITT analysis)

	Pre-procedure RVD ≥2.25 mm Median = 2.79 mm		Pre-procedure RVD <2.25 mm Median = 2.14 mm	
Endpoint	BVS (N = 224)	XIENCE (N = 117)	BVS (N = 41)	XIENCE (N = 17)
TLF	4.5% (10/223)	1.7% (2/116)	2.4% (1/41)	17.6% (3/17)
Cardiac death	0.0% (0/223)	0.0% (0/116)	0.0% (0/41)	0.0% (0/17)
TV-MI	3.6% (8/223)	1.7% (2/116)	2.4% (1/41)	5.9% (1/17)
ID-TLR	2.7% (6/223)	0.0% (0/116)	2.4% (1/41)	17.6% (3/17)
ST	1.4% (3/220)	0.9% (1/116)	2.4% (1/41)	5.9% (1/17)

Although Study AVJ-301 showed no clear tendency because of the limited number of subjects, 3 of 4 ST events reported through 12 months in the BVS group occurred in subjects treated with BVS with a diameter of 2.5 mm (RVD, 2.00-2.45 mm). The post-procedure minimal lumen diameter (MLD) in these subjects was as small as 1.51 to 2.05 mm. The remaining 1 ST event occurred in a lesion treated with BVS with a diameter of 3.0 mm, of which MLD was also as small as 2.11 mm (Table 39). These findings suggest that treatment of small blood vessels and inadequate stent dilatation are the risk factors for ST. Accurate measurement of the vessel diameter and adequate post-dilatation will, therefore, reduce the incidence of ST.

Table 39. Summary of ST events reported within 1 year in Study AVJ-301

ID ST Type	Time to onset from procedure (day)	Lesion site	Device size (mm)	QCA-RVD/ lesion length (mm)	Post-procedure MLD (mm)	Post-procedure use of imaging device	Post-dilatation	DAPT	Suspected cause
ST1 Definite	4	Mid RCA	2.5 × 18	2.45/13.8	D: 2.27 S: 2.05	OCT	Yes	Ongoing	Small MLD
ST2 Definite	139	Mid LAD	2.5 × 28	2.00/20.28	D: 1.84 S: 1.70	No	No	Both drugs discontinued at 3 months	Small RVD/MLD (inadequate dilatation), Interruption of DAPT
ST3 Definite	5	Dist LCX	2.5 × 18	2.32/12.7	D: 1.69 S: 1.51	OCT	No	Ongoing	Small RVD/MLD (inadequate dilatation)
ST4 Definite	4	Prox LAD	3.0 × 18	2.775/12.49	D: 2.40 S: 2.11	IVUS	Yes	Ongoing	Small MLD

Note) D, in-device; S, in-segment; %DS, % diameter stenosis

The sample size of Study AVJ-301 was determined to assess the non-inferiority of BVS, assuming the 12-month TLF rate of 7%. The results of this study should be interpreted carefully because the sample size is too small for a subgroup analysis of events with a low incidence, such as ST.

Tables 40 and 41 present cardiac events at the onset of ST and their outcomes in Study AVJ-301 and the ABSORB III study, respectively. In all subjects, ST (definite) was successfully treated. No cardiac death after treatment of ST was reported.

Table 40. Cardiac events at onset of ST and their outcomes in Study AVJ-301

	BVS N = 4	XIENCE N = 2
Cardiac events at onset of ST		
TV-QMI	75% (3/4)	50% (1/2)
TV-NQMI	25% (1/4)	50% (1/2)
Unstable angina pectoris	0% (0/4)	0% (0/2)
ID-TLR	100% (4/4)	50% (1/2)
Clinical outcome in subjects with ST		
Cardiac death	0% (0/4)	0% (0/2)
TV-MI	0% (0/4)	0% (0/2)
ST (ARC def/prob)	0% (0/4)	0% (0/2)
TVR	0% (0/4)	50% (1/2)
Re-hospitalization	0% (0/4)	50% (1/2)
No subsequent adverse event	100% (4/4)	0% (0/2)

Table 41. Cardiac events at onset of ST and their outcomes in the ABSORB III study (Based on actual treatment. Definite ST only.)

	BVS N = 17*	XIENCE N = 6
Cardiac events at onset of ST		
TV-QMI	47% (8/17)	17% (1/6)
TV-NQMI	35% (6/17)	67% (4/6)
Unstable angina pectoris	18% (3/17)	17% (1/6)
ID-TLR	100% (17/17)	100% (6/6)
Clinical outcome in subjects with ST		
Cardiac death	0% (0/17)	0% (0/6)
TV-MI	6% (1/17)	0% (0/6)
ST (ARC def/prob)	0% (0/17)	0% (0/6)
TVR	6% (1/17)	33% (2/6)
Re-hospitalization	35% (6/17)	67% (4/6)
No subsequent adverse event	59% (10/17)	33% (2/6)

Note) Definite ST was reported by 18 subjects in the BVS group, including 1 subject who was treated with XIENCE stent; definite ST was reported by 17 subjects in the BVS group. Probable ST was reported by 2 subjects in the BVS group and both subjects died from a cardiac cause within 30 days.

According to the network meta-analysis of 49 randomized studies (N = 50,844) performed by Palmerini et al. to compare the safety of first-generation DESs, second-generation DESs, and BMSs in patients with angina pectoris,[23] comparison of the incidence of ST (definite) between BMSs and XIENCE stents demonstrated that the XIENCE stents were associated with a significantly decreased incidence of ST (cumulative incidence through 1 year and 2 years, early incidence, and late incidence) compared to BMSs. The results indicate higher safety of XIENCE stents. The outcome of ST through 1 year with XIENCE stents in this network meta-analysis was compared with the outcome of ST in the ABSORB III study. The odds ratio of BVS to XIENCE stents in the ABSORB III study was 2.11, which was comparable to the results of comparison with other stents (odds ratio, 2.44-7.14). The safety of BVS, therefore, appears to be comparable to that of other stents in terms of the incidence of ST (definite) through 1 year (Figure 9).

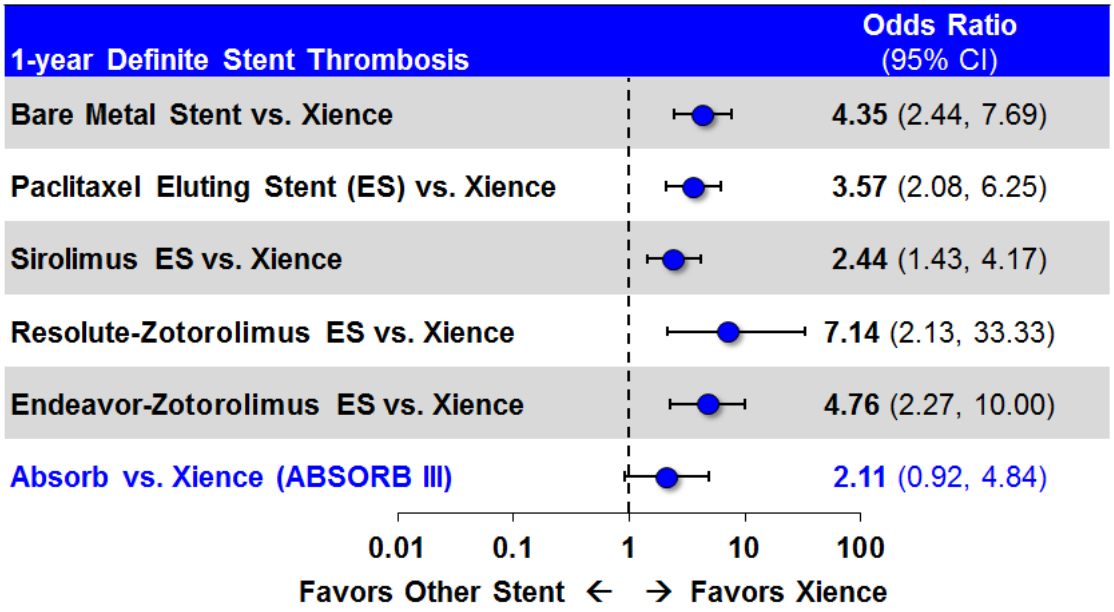


Figure 9. ST (definite) through 1 year
based on network meta-analysis and the ABSORB III study

PMDA's view:

ST is a known but serious adverse event associated with stent implantation. It is a major challenge to reduce the incidence of ST. The applicant has claimed, based on the post-marketing experience in Europe and the results of the meta-analysis, that Absorb GT1 BVS had no substantially higher incidence of ST within 1 year than approved DESs. The applicant's claim is understandable. However, ST associated with Absorb GT1 BVS was often accompanied by QMI. Considering the fact that all subjects underwent TLR, investigation of its causes and the development of countermeasures are essential.

The struts of Absorb GT1 BVS are characteristically thicker than those of usual metal stents. The post-procedure QCA results also showed that the BVS group had small in-device minimal lumen diameters and tended to have a high in-device % DS. A small vessel size is a risk factor for ST also in treatment with a metal stent. In subjects with a small vessel size, failure to achieve a sufficient post-procedure MLD may increase the risk of ST. In fact, a certain number of subjects included in the clinical studies had an RVD of <2.25 mm as measured by QCA despite their inclusion criterion of having an RVD of ≥2.5 mm, resulting in a trend toward a high incidence of ST. To achieve a sufficient MLD after placement of Absorb GT1 BVS, therefore, appropriate RVD measurement, proper device size selection, and sufficient post-dilatation appear to be effective to reduce the risk of ST after implantation of Absorb GT1 BVS. PMDA accepted the applicant's explanation that appropriate measurement of the diameter of the blood vessel with a target lesion and adequate post-dilatation are important to reduce the risk of ST. PMDA instructed the applicant to include the following 2 precautions in the method of use of Absorb GT1 BVS and the applicant agreed.

In principle,

(a) measure the RVD for the target lesion appropriately by a quantitative method (online QCA or intravascular diagnostic imaging [IVUS or OCT]) to select a proper device size, and

(b) check the apposition of Absorb GT1 BVS to the vascular wall by intravascular diagnostic imaging (IVUS or OCT) and, if necessary, perform post-dilation to achieve sufficient apposition.

In addition, whether the risk of ST is appropriately reduced by the proper procedure of Absorb GT1 BVS implantation should be verified in a post-marketing use-results survey that involves all patients treated with Absorb GT1 BVS for a certain period of time. The survey should verify whether ensuring the proper implantation procedure can prevent the occurrence of ST [see Condition of Approval 2 and Section "6.B.3. Post-marketing safety measures"]. PMDA concluded that the applicant should identify ST cases in cooperation with related academic societies, collect information on them, and analyze causes of ST, and that other conditions of approval should be added so that further risk reduction measures are taken, as necessary [Condition of Approval 3].

6.B.1.(1).2) Myocardial infarction

Table 42 summarizes acute MI cases in Study AVJ 301, and the ABSORB II and ABSORB III studies. None of the studies showed a significant difference between the 2 groups. The differences in overall TV-MI between the BVS and XIENCE groups were 1.14% in Study AVJ-301 and 1.44% in the ABSORB III study, while the difference was 3.02% in the ABSORB II study. The incidence of acute MI was numerically higher in the BVS group than the XIENCE group.

Of 14 TV-MI events noted in the BVS group in the ABSORB II study, 12 events were perioperative MI. Two events in the XIENCE group were also perioperative MI. All of these events were NQMI. BVS has a large strut width (≤0.22 mm for BVS, ≤[redacted] mm for XIENCE), which is more likely to occlude small side branches. This probably led to an increased risk for clinically insignificant MI. The incidence of MI from the perioperative period through 1 year was 0.6% (2 of 331 subjects) in the BVS group and 0.0% (0 of 165 subjects) in the XIENCE group. The difference between the BVS and XIENCE groups was large during the perioperative period.

The other known cause of MI is ST, which is often accompanied by QMI. As aforementioned, a relatively high incidence of ST in the BVS group was probably attributable to improper implantation procedures, which can be improved. Some MI cases after stent implantation were not associated with ST. In the ABSORB III study, the incidence of TV-MI not associated with ST was 4.9% in the BVS group and 4.0% in the XIENCE group, with a difference of 0.89%. In subjects with RVD of ≥2.25 mm, the incidence of TV-MI not associated with ST was 4.4% in the BVS group and 4.1% in the XIENCE group, with a difference of 0.35%.

In summary, perioperative MI may be attributable to the strut design, but would rarely lead to clinically relevant problems. As described above, MI associated with ST can be reduced by ensuring the proper implantation procedure. The incidences of other types of MI were similar in the BVS and XIENCE groups. For these reasons, the differences in the incidence of MI in these clinical studies are unlikely to pose significant safety concerns in the post-marketing setting. Nevertheless, as a risk reduction measure, the Instructions for Use should advise surgeon to avoid scaffolding across any side branches with a diameter of ≥2.0 mm as with the exclusion criteria of the clinical studies.

Table 42. Summary of MI events in pivotal clinical studies (through 1 year)

Study	Type of MI	BVS	XIENCE	Difference
Study AVJ-301	All TV-MI	3.4% (9/265)	2.3% (3/133)	1.14%
	- TV-QMI	1.1% (3/265)	0.0% (0/133)	1.13%
	- TV-NQMI	2.3% (6/265)	2.3% (3/133)	0.01%
	TV-MI not associated with ST	1.9% (5/265)	0.8% (1/133)	1.13%
ABSORB II study	All TV-MI	4.2% (14/331)	1.2% (2/165)	3.02%
	- TV-QMI	0.6% (2/331)	0.0% (0/165)	0.60%
	- TV-NQMI	3.6% (12/331)	1.2% (2/165)	2.41%
	TV-MI not associated with ST	3.3% (11/331)	1.2% (2/165)	2.11%
ABSORB III study	All TV-MI	6.0% (79/1313)	4.6% (31/677)	1.44%
	- TV-QMI	0.7% (9/1313)	0.3% (2/677)	0.39%
	- TV-NQMI	5.3% (70/1313)	4.3% (29/677)	1.05%
	TV-MI not associated with ST*	4.9% (64/1313)	4.0% (27/677)	0.89%
ABSORB III study RVD ≥2.25 mm	TV-MI not associated with ST*	4.4% (47/1066)	4.1% (22/542)	0.35%

Note) N = total number of enrolled subjects.
* Included definite ST events only because all probable ST events in the ABSORB III study resulted in death from unknown cause.

PMDA' view:

The applicant has claimed that there were tendency toward the higher incidence of MI in the BVS group than that in the XIENCE group because of the occlusion of side branches primarily during the perioperative period and ST. The applicant's claim is reasonable. Perioperative MI resulting from occluded side branches is a known adverse event associated with metal stents and is rarely clinically relevant. PMDA also accepted largely the applicant's opinion that the risk of MI can be reduced by advising surgeons to avoid scaffolding across any side branches and to comply with the aforementioned proper implantation procedure to reduce ST.

6.B.1.(1).3) Procedural problems identified in Study AVJ-301

In Study AVJ-301, it was difficult to pass a device, etc. through the implanted BVS (difficulty in passing-through) in 20 subjects. The details of the event are presented below. Eventually, a post-dilatation balloon, IVUS/OCT, other stents, etc. passed through 15 lesions in 15 subjects, and failed to pass through 6 lesions in 5 subjects. The total number of events was not consistent with the number of subjects because 1 of the subjects experienced more than 1 event of difficulty in passing-through.

- After difficulty in passing through, the post-dilatation balloon, IVUS, or OCT eventually passed through the implanted BVS: 14 events (by using a small and low profile standard balloon and buddy wire, or changing the guiding catheter)
- Failure to pass a post-dilatation balloon: 2 events
- Failure to pass IVUS: 3 events
- Failure to pass OCT: 1 event
- Eventual implantation of XIENCE Xpedition because of difficulty in passing-through the third BVS during bailout procedure: 1 case

As aforementioned, in 15 of 21 events of difficulty in passing-through, the devices eventually passed through BVS successfully. Difficulty in passing-through of a post-dilatation balloon appears to be clinically relevant because failure to achieve post-dilatation may cause inadequate dilatation or mal-apposition. In this study, 2 events of failure of a post-dilatation balloon to pass through the scaffold were reported eventually. In the study, post-dilatation was not actively recommended. In addition, surgeons

might not have taken further procedures when they felt difficulty in passing through the devices because there was a concern about strut damages due to IVUS/OCT. Surgeons probably had a difficulty in letting a device pass through the scaffold during bail-out procedure. Eventually, however, XIENCE Xpedition was implanted successfully. The subjects with difficulty in passing-through had satisfactory clinical outcome at 1 year, without experiencing TLF or ST. Neither strut fracture nor perioperative complication was reported in these subjects by any study site. In conclusion, difficulty in passing-through itself is unlikely to affect the clinical outcome of patients.

On the basis of the above results and foreign experience, the applicant plans to provide surgeons with skills training on measures to be taken in the case of difficulty in passing-through of other devices. As the use of a post-dilatation balloon in combination with IVUS/OCT is strongly recommended in post-marketing clinical settings, cases with difficulty in passing these devices through the implanted Absorb GT1 BVS may increase in number. Currently, aggressive pre-dilatation (lumen dilatation after BVS placement) is recommended, which is expected to reduce difficulty in passing-through.

On the basis of the above discussion, the safety risk is considered to be within the acceptable range. This event can be reduced by providing surgeons with appropriate training for implantation and by informing them of relevant countermeasures in training sessions. The status of the event will also be continuously focused on in the use-results survey.

PMDA's view:
The applicant's explanation is generally acceptable because neither TLF nor ST occurred in the subjects with difficulty in passing-through in Study AVJ-301. On the basis of the above information on malfunctions, however, the applicant should adequately advise surgeons on product malfunctions through training sessions and the Instructions for Use because difficulties in passing-through of a post-dilatation balloon, IVUS, or OCT were found in a certain number of patients in whom some additional intervention measures were necessary to pass them through the implanted scaffold in Study AVJ-301. The applicant agreed to do so.

6.B.1.(2) Efficacy and safety of Absorb GT1 BVS at ≥1 year

6.B.1.(2).1) Long-term outcome of each study

PMDA asked the applicant to explain the latest long-term outcomes with BVS.

The applicant's explanation about the long-term outcomes with BVS obtained as of July 2016:
Table 43 presents the long-term results from Study AVJ-301, and the ABSORB II and ABSORB EXTEND studies in terms of TLF and each event composing TLF at 2 years.

Table 43. Long-term clinical outcomes with AVJ-301 (ITT analysis)

TLF	Study AVJ-301		ABSORB II study		ABSORB EXTEND study
	BVS	XIENCE	BVS	XIENCE	
1-Year					
TLF	4.2% (11/265)	3.8% (5/133)	4.8% (16/331)	3.0% (5/165)	5.1% (41/811)
Cardiac death	0.0% (0/265)	0.0% (0/133)	0.0% (0/331)	0.0% (0/165)	0.7% (6/811)
TV-MI	3.4% (9/265)	2.3% (3/133)	4.2% (14/331)	1.2% (2/165)	3.3% (27/811)
ID-TLR	2.6% (7/265)	2.3% (3/133)	1.2% (4/331)	1.8% (3/165)	2.3% (19/811)
2-Years					
TLF	7.3% (19/261)	3.8% (5/130)	7.0% (23/328)	3.0% (5/164)	7.1% (57/807)
Cardiac death	0.4% (1/261)	0.0% (0/130)	0.6% (2/328)	0.0% (0/164)	1.1% (9/807)
TV-MI	5.0% (13/261)	3.1% (4/130)	5.2% (17/328)	1.2% (2/164)	4.2% (35/807)
ID-TLR	5.4% (14/261)	2.3% (3/130)	2.7% (9/328)	1.8% (3/164)	4.2% (34/807)

Note) N = total number of enrolled subjects.

Overall, the incidence of TLF and that of each event related to TLF were comparable among these 3 studies. The BVS and XIENCE groups had a very similar incidence of TLF at 2 years among the 3 studies, indicating no ethnic difference. In Study AVJ-301 and the ABSORB II study, the BVS group had a higher incidence of TLF than the XIENCE group. Considering that most surgeons experienced intervention with BVS for the first time in these studies, however, the above result is acceptable. For example, the median number of patients treated with BVS implantation per surgeon is 2 (a maximum of 10) in Japan, while an estimated several hundreds of patients were treated with XIENCE stent implantation over several years. The BVS group had an approximately 2% to 3% increase in the incidence of TLF from 1 year to 2 years, which was comparable to the % increase (2%) in the incidence of TLF from 1 year to 2 years in the SPIRIT III study, a first large-scale clinical study evaluating XIENCE stent, suggesting that the results in the BVS group were reasonable. In addition, no recommended appropriate implantation procedure had been established yet at the time of designing and conducting Study AVJ-301 because no sufficient knowledge based on the experience in other clinical studies or with similar commercial products had been accumulated.

In Study AVJ-301, TLF events were reported in 8 subjects between the 1-year and 2-year follow-ups (cardiac death in 1 subject, MI/ID-TLR associated with VLST occurring at ≥1 year in 4 subjects, ID-TLR associated with re-stenosis in 3 subjects). In the BVS group, 3 subjects experienced ID-TLR associated with re-stenosis. These subjects were asymptomatic and underwent TLR because scheduled angiography identified re-stenosis of the target lesion. Of the 3 subjects, 2 had a % DS of ≥70% (73% and 78%), while the remaining 1 subject had a % DS of approximately 50%, but was positive for FFR. In addition, the 2-year follow-up angiography revealed NID-TLR in 1 subject. In the XIENCE group, new TLR was reported in 2 subjects between the 1-year and 2-year follow-ups. Both subjects were diagnosed with NID-TLR.

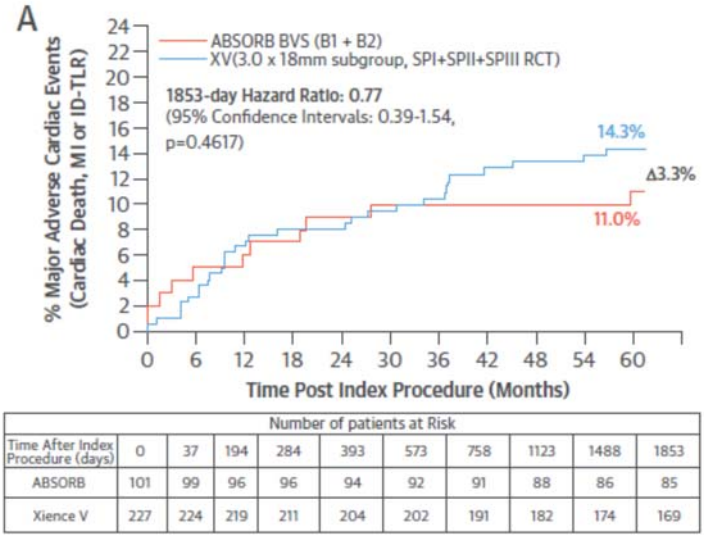
PMDA asked the applicant to explain whether the study results with Absorb GT1 BVS at ≥1 year were clinically acceptable in current clinical settings in Japan.

The applicant's explanation:
Cypher stent, the first DES introduced into Japan, was approved on the basis of the PK data from 30 Japanese subjects. Most Japanese surgeons had the first experience with a DES in the use-results survey of Cypher stent conducted after its marketing (Cypher PMS) (registration period, September 2004 to September 2005). The survey revealed the incidence of TVF (composite event of cardiac death, TV-MI, and TLR) of 9.6% at 1 year, which increased by 3.9% to 13.5% at 2 years (an increase of 3.1% in the BVS group in Study AVJ-301).[24]

In the RESET study that compared XIENCE V and Cypher stents (registration period, February 22 to July 30, 2010), which was conducted involving Japanese surgeons with several-year experience with the use of Cypher stent, the Cypher group had an incidence of TLF (composite event of cardiac death, TV-MI, and ID-TLR) of 7.7% at 1 year and 9.7% at 2 years.[25] Since TLF in the RESET study only included ID-TLR, the incidence of TVF in this study is inferred to show a 0.5% to 0.8% increase when calculated by the definition of TVF in Cypher PMS (composite event of cardiac death, TV-MI, and TLR). This estimation showed an improvement in the incidence of TVF in Cypher PMS (1-year outcomes, 9.6% in Cypher PMS versus 8.5% [estimation] in the RESET study; 2-year outcomes, 13.5% in Cypher PMS versus 10.5% [estimation] in the RESET study). Accumulated experience of surgeons from Cypher PMS until the RESET study was likely to have led to the improved outcome.

In conclusion, the incidence of TLF of 7.3% in the BVS group is acceptable for the first randomized clinical study of BVS in Japan (median number of patients treated with BVS implantation per surgeon, 2 patients). With appropriate procedures and accumulated experience with BVS, the incidence of the event is expected to decrease over time.

Comparison of the results of the ABSORB Cohort B and XIENCE V studies, of which 5-year follow-up was completed, by the propensity score match method was reported. The BVS group tended to have a decreased incidence of MACE (without a statistically significantly difference) at ≥3 years when the scaffold skeleton disappears (Figure 10).[26] Although there is a limitation to retrospective analysis, this analysis showed the non-inferiority of BVS to DES when the baseline characteristics of the 2 studies were matched by the propensity score match method. The analysis has a high clinical significance in that it showed that BVS was associated with a similar outcome to XIENCE stent and a decreased incidence of late events.



Number of patients at Risk										
Time After Index Procedure (days)	0	37	194	284	393	573	758	1123	1488	1853
ABSORB	101	99	96	96	94	92	91	88	86	85
Xience V	227	224	219	211	204	202	191	182	174	169

Figure 10. Comparison of the results of the ABSORB Cohort B and XIENCE V studies by propensity score match method

PMDA's view:

Although the BVS group tended to have a higher incidence of TLF at ≥1 year than that of the XIENCE group in Japanese Study AVJ-301, the long-term outcome with BVS was clinically acceptable for the following reasons: (i) The BVS group had an approximately 2% to 3% annual increase in the incidence of TLF, which was similar to the annual increase in the incidence of TLF from 1-year to 2-year follow-ups (2%) in the SPIRIT III study which was the first large-scale clinical study evaluating XIENCE stent, and (ii) a possible reduction in the incidence of VLST may decrease the incidence of TLF at 1≥ year because approximately half the increase in the incidence of TLF events occurring at ≥1 year were associated with MI/ID-TLR resulting from VLST [see Section "6.B.1.(2).2) VLST"].

6.B.1.(2).2) VLST

The applicant's explanation about ST and VLST associated with the use of BVS:

Table 44 presents the incidences of ST and VLST in each study.

Table 44. Incidences of ST and VLST associated with the use of AVJ-301

	Study AVJ-301		**ABSORB II study**		**ABSORB EXTEND study**
	BVS	XIENCE	BVS	XIENCE	
1-Year	1.5% (4/262)	1.5% (2/133)	0.9% (3/329)	0.0% (0/164)	1.0% (8/808)
2-Year	3.1% (8/257)	1.5% (2/130)	1.5% (5/325)	0.0% (0/163)	1.5% (12/800)
3-Year	NA	NA	NA	NA	1.9% (12/630*)

* Some subjects did not complete the 3-year follow-up.
Note) N = total number of enrolled subjects.

In Study AVJ-301, VLST was reported in 4 subjects at 1 year and 2 years post-procedure only in the BVS group; VLST was reported in 1 subject at ≥2 years, but the study results at 3 years have not been finalized yet. Comparison with a series of ABSORB studies showed no statistical difference between Japanese and non-Japanese subjects (Table 45). Since Study AVJ-301 in 400 subjects was intended to

demonstrate the non-inferiority of BVS in terms of the incidence of TLF at 1 year assuming the true incidence of 9.4%, the results of events with a low incidence should be carefully interpreted.

Table 45. Incidence of VLST in ABSORB studies

Study	VLST (Years 1-2)	*P* = value*
ABSORB Cohort B	0.0% (0/101)	
ABSORB EXTEND study	0.5% (4/812)	
ABSORB II study	0.6% (2/335)	[redacted]
Study AVJ-301	1.5% (4/267)	
ABSORB III study	[redacted]**	

* Fischer's exact test

** The incidence of VLST was calculated using the total number of events in the BVS and XIENCE groups as the worst case because this study is in the blind phase. [redacted]
No subjects excluded from the analysis experienced ST.

Details of VLST in Study AVJ-301

ST reported within 1 year primarily occurred in small blood vessels, while VLST occurred with stents with a diameter of 3.0 and 3.5 mm, suggesting a different mechanism of onset between ST reported within 1 year (mainly within 30 days) and VLST.

Taniwaki et al. identified risk factors for VLST on the basis of OCT findings after implantation of a metal stent. Mal-apposition, neoatherosclerosis, incomplete coverage, and poor dilatation were major risk factors.[27] Table 46 summarizes the results of intravascular imaging analysis at the onset of VLST in Study AVJ-301. Mal-apposition of struts, poor dilatation, and incomplete coverage of struts were observed, which were consistent with the findings with the metal stent reported by Taniwaki et al. (as well as the OCT/IVUS findings of VLST in the ABSORB II study where intravascular images were obtained as in Study AVJ-301). Table 47 presents cardiac events at the onset of VLST and their outcomes.

Table 46. Summary of VLST in Study AVJ-301

	Time to onset (day)	Lesion location	Device (mm)	Diagnostic imaging after implantation	Post-dilatation	DAPT	Suspected cause
VLST1 Definite	494	Prox LAD	3.5 × 28	OCT 2 subgroup: No	Yes	Aspirin: Discontinued 1 week before onset of the event Clopidogrel: Discontinued at ≥1 year	Marked mal-apposition at the proximal end of the scaffold
VLST 2 Definite	679	Dist RCA	3.5 × 18	OCT 2 subgroup: No	No	Aspirin: Continued Clopidogrel: Discontinued at 669 days	Undersize (the vessel diameter was 3.11 mm as measured by pre-procedure QCA at the core lab, but appeared to be approximately 3.75 to 4.00 mm during re-assessment), inadequate dilatation, and mal-apposition
VLST 3 Definite	536	Prox RCA	3.5 × 18	IVUS subgroup: IVUS	No	Clopidogrel: Discontinued at ≥1 year Aspirin: Interrupted for 2 months	Undersize (the vessel diameter was approximately 4.2 mm during re-assessment of pre-procedure IVUS) and inadequate dilatation
VLST 4 Definite	595	Dist RCA	3.0 × 18	OCT 2 subgroup: No	Yes	DAPT: Continued	An untreated lesion was found distal to the target lesion during the procedure in the clinical study. The rupture of this untreated lesion might have caused thrombosis. OCT 16 days after the onset of thrombosis showed patent BVS without a thrombus, but mal-apposition at the edge.
VLST 5 Definite (under review*)	810	Dist RCA	3.5 × 18	OCT 2 subgroup: No**	Yes	Aspirin: Continued Clopidogrel: Discontinued at 669 days	Undersize and inadequate dilatation (tapered blood vessel with a difference of 1.3 mm) No mal-apposition (with neointimal growth)

* This may be changed depending on the results of CEC's assessment.

** The subject was allocated to the OCT 2 subgroup that received no post-procedure diagnostic imaging, but underwent post-procedure IVUS at investigator's discretion.

Table 47. Cardiac events at onset of VLST and their outcomes in Study AVJ-301

	BVS N = 5	XIENCE N = 0
Cardiac events at onset of ST		
TV-QMI	40% (2/5)	-
TV-NQMI	40% (2/5)	-
No MI (unstable angina pectoris)	20% (1/5)	-
ID-TLR	100% (5/5)	-
Outcome		
Cardiac death	0% (0/5)	-
TV-MI	20% (1/5)*	-
ST	0% (0/5)	-
TLR	0% (0/5)	-

* TLR was reported in 1 subject with VLST. This subject was treated with a balloon alone without stent implantation for the treatment of VLST at 679 days to maintain the benefits of Absorb GT1 BVS. Although the treatment was successful, angina pectoris recurred 2 days later because of insufficient efficacy. The subject underwent stent implantation at 25 days after the treatment of VLST.

In Study AVJ-301, subjects were allocated to one of 3 imaging subgroups: the IVUS subgroup receiving post-procedure IVUS, the OCT 1 subgroup receiving OCT, or the OCT 2 subgroup receiving no post-procedure intravascular diagnostic imaging (Figure 6). This process was intended to confirm that

intravascular diagnostic imaging devices did not damage BVS struts. Since the fracture of struts due to over-dilatation was the most significant concern at the start of the study, additional dilatation after IVUS/OCT was not recommended and the second post-dilatation was allowed only when substantial mal-apposition was observed. Under this protocol, which imaging modality was assigned to each subject was unknown before the procedure in Study AVJ-301, and consequently, concomitant IVUS for measurement of the baseline vessel diameter was used in as low as 13.8% of the subjects. A publication has reported that image-guided stent implantation procedures account for ≥80% of the PCI procedures used in routine clinical practice in Japan.[28] The implantation procedure in Study AVJ-301 appears to be inconsistent with that in routine clinical practice.

Table 48 presents the status of post-dilatation in each subgroup. Of 4 subjects with VLST in the OCT 2 subgroup which underwent no post-procedure diagnostic imaging, 1 received no post-dilatation. OCT images in this subject at the onset of VLST confirmed inadequate dilatation. The remaining 3 subjects received high-pressure post-dilatation. Imaging at the onset of VLST, however, showed mal-apposition in 1 subject of them and inadequate dilatation in another subject. The remaining 1 subject in the OCT 2 subgroup may have had thrombus caused by aggravation/rupture of a distal lesion that was not treated during the study procedure. The thrombus was unlikely to be directly associated with AVJ-301. The results of 2-year OCT in the OCT 1 subgroup showed no late mal-apposition. Mal-apposition later observed in the subject with VLST is inferred to have occurred during the procedure. No VLST occurred in any subject who underwent post-dilatation with an intravenous diagnostic imaging device.

In conclusion, appropriate post-dilatation according to the established clinical procedures in Japan to achieve complete dilatation and good apposition is expected to reduce the occurrence of VLST.

Table 48. Status of post-dilatation in each post-procedure intravenous diagnostic imaging group

	IVUS (L = 103)	OCT 1 (L = 86)	OCT 2 (L = 86)
No post-dilatation	13 (13%)	20 (23%)	14 (16%)
Post-dilatation	90 (87%)	66 (77%)	72 (84%)
No. of frequency of post-dilatation			
1	59 (65%)	46 (69%)	51 (71%)
2	29 (32%)	17 (26%)	20 (28%)
3	1 (1%)	3 (5%)	1 (1%)
4	1 (1%)	0	0
Balloon inflation pressure for post-dilatation	15.23 ± 4.25	15.20 ± 4.15	16.1 ± 4.0
Balloon diameter during post-dilatation	3.18 ± 0.47	3.14 ± 0.44	3.22 ± 0.40

PMDA's view:

VLST occurred mainly in blood vessels other than small vessels. Since VLST may result in more serious adverse events, it should be treated more carefully. The risk of VLST in Japan is described below.

- The ABSORB III study is currently in the blind phase. According to interim analysis of [redacted] subjects who completed 2-year follow-up, [redacted] subjects experienced VLST. Even if all of them were observed in the BVS group, the incidence of VLST is [redacted]% ([redacted] subjects), which is comparable to the incidence (0.4%, 669 subjects) in the XIENCE group in the SPIRIT III study. The incidence of VLST was 0.0% (0 of 101 subjects) in ABSORB Cohort B, 0.5% (4 of 812 subjects) in the ABSORB EXTEND study, and 0.6% (2 of 335 subjects) in the ABSORB II study. The applicant

explained that the risk for VLST with Absorb GT1 BVS is comparable to that with approved DESs, and such explanation is acceptable.

- In Study AVJ-301, VLST occurred in 5 subjects in the AVJ-301 group at ≥1 year, but not in any of the subjects in the XIENCE group. The applicant discussed the following interpretation: The protocol of this study did not proactively recommend post-dilatation because the concern at the start of the study was a potential significant risk associated with the fracture of struts due to over-dilatation, nor did it allow post-procedure intravascular diagnostic imaging in the OCT 2 subgroup; these might have led to the use of different procedures from the image-guided stent implantation procedures established in clinical practice in Japan, resulting in the increased incidence of VLST.
  The applicant has claimed that in order to prevent the occurrence of VLST, it is important to select an appropriate stent size and perform image-guided post-dilatation to achieve complete dilatation and good apposition. The applicant's claim is generally reasonable because (1) the detailed data, including diagnostic images from individual subjects with VLST in Japan, suggest that the cause of VLST was inadequate dilatation, mal-apposition, and under stent site, although no clinical data are available in Japan for Absorb GT1 BVS implanted by an image-guided procedure as in clinical practice; (2) 2-year OCT findings in the OCT 1 subgroup subjected to post-procedure OCT showed no late mal-apposition; and (3) VLST did not occur in the OCT 1 subgroup.

On the other hand, there is no data supporting these risk reduction measures actually reducing the incidence of VLST to a similar level to that in Europe and the US. Therefore, the risk of VLST should be reduced as much as possible by ensuring the proper use of Absorb GT1 BVS, for example, by providing skills training and information on VLST, in cooperation with related academic societies. The appropriateness of the proposed risk reduction measures should be assessed in a post-marketing use-results survey. In addition, collected information on VLST and the annual reports from the clinical studies should be reviewed to analyze the causes of the event and consider the necessity of a new risk reduction measure, as needed, to establish a system that appropriately addresses problems [Conditions of Approval 1, 3, and 4]. To collect information on VLST associated with the bioresorbable scaffold, which is expected to be introduced in Japan for the first time, and to ensure that risk reduction measures are taken carefully, the stepwise introduction of Absorb GT1 BVS is preferable. PMDA concluded that the potential risk of VLST associated with Absorb GT1 BVS after the risk reduction measures were taken would be clinically acceptable, provided that appropriate post-marketing safety measures were taken on the basis of the above discussion. The post-marketing safety measures are evaluated also considering the information described later in Section "6.B.3. Post-marketing safety measures."

6.B.1.(3) Safety of additional interventions

The applicant's explanation about the safety of additional interventions with Absorb GT1 BVS is presented in sections below.

6.B.1.(3).1) Scheduled overlapping implantation

A total of 2799 subjects were enrolled in the series of clinical studies for BVS, of which 272 subjects (9.7%) received overlapping implantation; 145 were subjected to scheduled overlapping implantation

and 127 were subjected to bailout implantation (89 with overlapping implantation of BVS, 37 with overlapping implantation of conventional DES) (Table 49).

Table 49. Summary of overlapping implantation of BVS in ABSORB studies

Study	No. of subjects treated with BVS	Total No. of overlapping implantation	Scheduled overlapping implantation	Bailout		
				Total	BVS	DES
ABSORB Cohort A	30	4	0	4	0	4
ABSORB Cohort B	101	6	0	6	0	6
ABSORB EXTEND study	812	119	85	34*	17	16
ABSORB II study	335	66	57	9	9	0
Study AVJ-301	266	5	0	5	4	1
ABSORB III study	1255	72	3	69	59	10
Total	2799	272	145	127	89	37

* The type of a device used for overlapping implantation is unknown in 1 subject.

Note) In Study AVJ-301 and the ABSORB III study, there was no scheduled overlapping implantation, but overlapping implantation was performed for bailout purposes. Scheduled overlapping implantation was performed in the ABSORB EXTEND and ABSORB II studies.

The incidence of MACE at 1 year was 11.0% in the overall subject population with overlapping implantation of BVS (Table 50), which was slightly higher than the results (4% to 9%) in the entire series of the clinical studies of BVS. MI was the predominant event among those composing MACE. Overlapping implantation increases the total length of the scaffolds and consequently increases the risk of occlusion of a side branch, which may result in perioperative MI. The incidence of ST was also slightly high (1.8%). With metal stents, overlapping implantation appears to be a predictive factor of ST.

Based on the above, the clinical outcome in subjects with overlapping implantation of BVS was predicted. Currently available information is, however, not sufficient to recommend scheduled overlapping implantation. Overlapping implantation should be allowed only for bailout purposes.

Table 50. One-year clinical outcome in subjects who underwent overlapping implantation of BVS in ABSORB studies

	Year 1 clinical outcome			
	MACE	ID-TLR	MI	ST
Scheduled overlapping implantation	10.4% (15/145)	2.1% (3/145)	10.3% (15/145)	2.1% (3/145)
Bailout with BVS	12.4% (11/89)	3.4% (3/89)	11.2% (10/89)	2.2% (2/89)
Bailout with DES	10.8% (4/37)	0.0% (0/37)	9.1% (3/37)	0.0% (0/37)
Total	11.0% (30/272)	2.2% (6/272)	10.3% (28/272)	1.8% (5/272)

Note) N = total number of enrolled subjects.

6.B.1.(3).2) Early revascularization after implantation of Absorb GT1 BVS

Of 2799 subjects enrolled in the series of BVS clinical studies, 40 subjects underwent early re-interventions for the target lesions implanted with BVS. The incidence of early TLR, which was defined as TLR occurring at <180 days, was as low as 1.4% (40 of 2799 subjects).

Table 51 presents the summary of interventions for early TLR in the 40 subjects.

Table 51. Summary of early TLR in ABSORB studies

	Subjects implanted with BVS	Early TLR	Intervention					
			Thrombus suction	Thrombus suction + balloon	Thrombus suction + stent	Only balloon	Only stent	Unknown or others
ABSORB Cohort A	30	1					1	
ABSORB Cohort B	101	3					3	
ABSORB EXTEND study	812	6	1	1	1		2	1
ABSORB II study	335	2			1		1	
Study AVJ-301	266	4	1		1	1	1	
ABSORB III study	1255	24		1	5	2	14	2*
Total	2799	40	2	2	8	3	22	3

* "Unknown or others" interventions were "unknown" for 1 subject, drug therapy for 1 subject, and CABG for 1 subject.

Note) The information on interventions shown above was based on the reports submitted by the study sites. Thrombus suction may not have been documented in the reports even when it was actually performed prior to stent implantation.

Postoperative complications were reported only in 3 of 40 subjects with early TLR, all of which were perioperative NQMI. In the remaining 37 subjects, the interventions were completed without any postoperative complications such as peripheral embolus. Of the 40 subjects, only 3 underwent re-TLR after the first TLR for interventions for re-stenosis but not ST. Three deaths (cause of death, unknown) occurred during the follow-up despite successful TLR; lung embolus at 46 days; Hodgkin's disease at 888 days; and ST-elevation myocardial infarction (STEMI) resulting from ST at 75 days. A causal relationship to the surgical procedure or study device was ruled out by the investigators.

6.B.1.(3).3) Outcome of additional late interventions

(a) Acute safety of TLR at ≥180 days

A total of 62 TLR events were reported at ≥180 days (7 events in ABSORB Cohort B, 34 events in the ABSORB EXTEND study, 2 events in the ABSORB II study, 16 events in the ABSORB III study, 3 events in Study AVJ-301) (as of September 2015). Of these, 3 subjects underwent TLR by CABG, while the remaining 59 subjects underwent TLR by PCI. None of these 59 subjects experienced any perioperative TLF event. Perioperative complications were reported in 4 subjects, 3 of whom experienced arterial dissection that was treated during the TLR procedure. The remaining 1 subject experienced angiospasm, bradycardia, and hypotension after removal of a sheath. The investigator reported that none of these events were related to the study device. Although the number of subjects who were treated with TLR at ≥180 days is limited, no finding that poses concerns on acute safety of Absorb GT1 BVS was observed.

(b) Recurrence of MACE after first TLR

Interventions for in-stent restenosis (ISR) are known to be a predictive factor of MACE also in the treatment with DESs. The PMS of XIENCE V conducted in Japan revealed that the hazard ratio for 1-year MACE with ISR interventions to that for interventions for *de novo* lesions was 2.74 (95% CI [1.66, 4.53]).

In ABSORB Cohort B and the ABSORB EXTEND study, 41 subjects underwent the first TLR at ≥180 days, and the incidence of MACE through 1 year after the first TLR was 10.6%. The incidence of 1-year MACE in the overall population for each study was 6.9% (7 of 101 subjects) in ABSORB Cohort B and 5.0% (41 of 812 subjects) in the ABSORB EXTEND study. The incidence of MACE based on the pooled data from both studies was 5.3% (49 of 913 subjects). When this value is compared with the

incidence of MACE through 1 year after the first TLR (10.6%), the hazard ratio is 2.0. The incidence of MACE through 1 year after the first TLR of 10.6%, therefore, appears to be reasonable. None of the 21 subjects who underwent TLR at ≥180 days in the ABSORB II and ABSORB III studies, and Study AVJ-301 experienced MACE although no data from these subjects are available regarding the long-term follow-up (≥180 days) after the first TLR.

PMDA's view on the safety of additional interventions:
The applicant has claimed that re-interventions will not cause any particular problem, after assessing the risk of scaffold fracture by re-interventions on the basis of the data obtained during bailout procedures, early re-interventions up to 6 months before intimal coverage of the scaffold, and late re-interventions at >6 months in the clinical studies as well as the non-clinical data. The applicant's claim is reasonable. Since the risk of re-interventions appears to be comparable to that with approved metal stents, it is clinically acceptable. On the basis of the 1-year MACE rate of 11% and the 1-year thrombosis rate of 1.8% after scheduled overlapping implantation, the applicant has decided that scheduled overlapping implantation is not recommended and that overlapping implantation should be allowed only for bailout procedures. The applicant's decision is reasonable.

6.B.2. Anti-platelet therapy

Considering that Absorb GT1 BVS may be associated with an increased risk for ST or VLST, PMDA asked the applicant to explain the recommended duration of DAPT.

The applicant's explanation:
The protocol of Study AVJ-301 specified the 12-month DAPT. During the study, 97.0% of subjects were on DAPT at 365 days (± 7 days). The safety of DAPT remains unknown when the therapy is discontinued at <12 months. It is, therefore, reasonable to recommend administering anti-platelet therapy with aspirin for an indefinite period of time and a thienopyridine anti-platelet agent for ≥12 months in patients treated with Absorb GT1 BVS.

In Study AVJ-301, VLST occurred in 5 subjects, including those who experienced the event at ≥2 years. Although prolonged DAPT might have been able to prevent VLST in these subjects, 98% strut coverage was achieved at 6 months in ABSORB Cohort B. Not all patients may require prolonged DAPT only if Absorb GT1 BVS is appropriately implanted.

Overall, physicians should decide the necessity of >1-year DAPT and the type of DAPT, considering the risk factors for VLST and hemorrhage in each patient.

PMDA's view:
The use of DAPT for ≥12 months post-implantation should be recommended in the Instructions for Use, based on the recommended duration of DAPT in the clinical studies, and physicians should decide the continued use of DAPT according to the patient's condition. In addition, the applicant should collect necessary information, including the causes of VLST and risks associated with prolonged DAPT, from long-term data and the data to be gathered through the post-marketing use-results survey of Absorb GT1 BVS in Japan in the future, and provide such information to healthcare professionals.

6.B.3. Post-marketing safety measures

PMDA asked the applicant to explain post-marketing safety measures necessary for introduction of Absorb GT1 BVS into Japan as a more effective and safer medical device than conventional stents, including (a) development of criteria for the qualification of surgeons and medical institutions for the use of Absorb GT1 BVS, (b) validation of the planned risk reduction measures, and (c) the necessity of a stepwise distribution plan.

The applicant's explanation:

Since implantation of Absorb GT1 BVS requires full understanding of its characteristics and full knowledge about the appropriate implantation procedures, treating surgeons must take training sessions. The distribution of Absorb GT1 BVS will be expanded in a stepwise manner while confirming that the appropriate implantation procedures for and proper use of the device reduces the incidence of ST. More specifically, Absorb GT1 BVS will be distributed to a limited number of medical institutions (approximately [redacted]), where all patients treated with Absorb GT1 BVS in the post-marketing setting will be registered in the use-results survey until the number of the patients registered reaches 2000. This use-results survey will be conducted in a 2-phase manner in cooperation with related academic societies. Phase 1 (approximately [redacted] medical institutions for up to 250 patients) is intended to assess the effectiveness of skills training. Phase 2 (approximately [redacted] medical institutions for up to 2000 patients including those participating in Phase 1) is intended to confirm that compliance with the appropriate implantation procedures reduces the incidence of ST. Phase 1 of the survey will be conducted at the medical institutions that have participated in Study AVJ-301 or by surgeons who have experience with Absorb GT1 BVS (or its previous versions) in and outside Japan. Phase 2 of the survey will be conducted at medical institutions to which specialists certified by the Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT) belong and which accept ≥100 patients with coronary artery lesions per year as well as medical institutions participating in Phase 1. Below are the basic requirements for medical institutions to participate in this survey:

(1) Treating surgeons must participate in seminars on the proper use of Absorb GT1 BVS and the recommended implantation procedures or similar briefings at medical offices (hereinafter collectively referred to as "seminars").

(2) A doctor or applicant's employee who has full knowledge of Absorb GT1 BVS must be present during the surgery of the first 3 patients for each surgeon, unless the medical institution has a surgeon with sufficient experience with the use of Absorb GT1 BVS (in ≥20 patients).

(3) Participating medical institutions must have an intravascular diagnostic imaging system (IVUS or OCT) and a surgeon with a thorough knowledge of image-guided PCI.

Outline of Seminars

- Overview of Absorb GT1 BVS
- Precautions regarding product handling
- Clinical study results
- Proper use of Absorb GT1 BVS

- Recommendations and verification method for proper implantation
- Promotion for registration in J-PCI registry
  (classroom lecture, approximately 2-3 hours)

The occurrence of thrombosis at 3 months post-procedure will be assessed in 2000 patients participating in Phase 1 or 2 of the survey. Reduction of thrombosis by the proper implantation procedure is considered successful when the incidence of thrombosis is ≤0.9%. The value was determined based on the incidence of ST, excluding small vessel thrombosis, in the ABSORB III study. Then, distribution of Absorb GT1 BVS to medical institutions other than those participating in the use-results survey will be started. To ensure compliance with the proper use of Absorb GT1 BVS, however, it will be distributed only to medical institutions that meet qualification criteria for a certain period of time. The qualification criteria include the aforementioned basic requirements and the following:

(4) Surgeons must provide consent to submit detailed information, including diagnostic images, on patients with thrombosis for proper risk management of Absorb GT1 BVS and investigation of causes of thrombosis.

(5) Medical institutions must have surgeons certified by the Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT). Also, qualified CVIT-certified surgeons must participate in the patient registration program.
Promotion of patient registration in the J-PCI registry during seminars and educational campaigns for patient registration by related academic societies are planned.

The applicant plans to carefully expand the distribution of Absorb GT1 BVS to medical institutions other than those participating in the use-results survey in a stepwise manner until a certain amount of information on VLST is collected, in order to provide information in a timely manner and ensure compliance with the risk reduction measures. The following steps will be taken.

- Post-marketing Phase 1:
  - The number of institutions to which Absorb GT1 BVS is distributed will be increased by [redacted] per month on average until the completion of 2-year follow-up of 250 patients enrolled in the use-results survey.

  - The next phase will be started if the incidence of ST and VLST is ≤1.5% (0.6% for VLST) at the completion of 2-year follow-up of 250 patients enrolled in the use-results survey. If the incidence exceeds 1.5%, whether to proceed to the next phase will be discussed with the regulatory authority, advisors, and related academic societies.

- Post-marketing Phase 2:
  - The number of institutions to which Absorb GT1 BVS is distributed will be increased by [redacted] per month on average until the completion of 2-year follow-up of 2000 patients enrolled in the use-results survey.

The applicant intends to discuss the aforementioned marketing plan which limits medical institutions with the regulatory authority, advisors, and related academic societies (e.g., CVIT) based on the results of the use-results survey and marketing conditions and review the plan. To ensure the safety of Absorb GT1 BVS, the applicant plans to perform trend analysis on the post-marketing incidence of ST and VLST, and take appropriate measures, such as market withdrawal, if the analysis shows an upward tendency of the incidence. When patients experience ST or VLST reported in the use-results survey, the procedures shown below will be followed. For instance, as much data as possible, including imaging information, will be collected from patients with these events even after the end of the survey period for causal analysis and risk reduction measures will be taken.

Method for reviewing ST and VLST events

ST and VLST events reported in the use-results survey will be reviewed not by participating medical institutions but by the Thrombosis Review Committee (consisting of surgeons participating in the post-marketing use-results survey, core lab doctors, and external experts as necessary) in cooperation with academic societies. The committee will assess the relationship with the device, complexity of lesions, and causes of ST and VLST based on collected diagnostic images, baseline characteristics of patients, and other appropriate data, and report the review results to participating medical institutions to reduce the risk of ST and VLST.

Provision of information to healthcare professionals

To provide information on the cases of ST and VLST reported, an advice document will be periodically created once a month in the early post-marketing stage, as with safety information for approved DES products, based on data reported to the regulatory authority. Knowledge (e.g., characteristics of patient with ST and ST events, possible causes, and recommendations) obtained from the Thrombosis Review Committee will also be added to the aforementioned document. In seminars, previously used information will be provided to medical institutions to which Absorb GT1 BVS is newly distributed, so as to promote the proper use of Absorb GT1 BVS.

The applicant will make every effort to ensure that treating surgeons comply with the guidelines for proper use developed by related academic societies, including the primary use of Absorb GT1 BVS in lesions similar to those treated in the clinical studies, until a certain level of clinical evidence is accumulated. To achieve this, following the completion of enrollment of 2000 patients in the use-results survey, large-scale investigator-initiated clinical research will be conducted, in cooperation with related academic societies, based on continued registration of patients at medical institutions participating in the use-results survey to continuously assess Absorb GT1 BVS ([redacted] according to the current plan). Although the sample size and endpoints may be changed according to the outcome of the use-results survey, [redacted] patients ([redacted] including 2000 patients participating in the use-results survey) will be included in this clinical research to accumulate evidence supporting the efficacy and safety of Absorb GT1 BVS in Japan and provide the evidence to healthcare professionals.

PMDA asked the applicant to provide the justification for proceeding to the post-marketing phase after confirmation of a reduction in the incidence of ST at 3 months.

The applicant's explanation:
ST events that occurred within 1 year were assessed. Of 4 events reported in Study AVJ-301, 3 occurred within 5 days (the remaining 1 event occurring at 139 days after discontinuation of DAPT). All of 19 events reported in the ABSORB III study occurred within 3 months, indicating that reduction in the occurrence of ST within 3 months will lead to a reduced overall incidence of ST, including VLST. Whether the incidence of VLST is reduced will be assessed in the post-marketing phase. The stepwise expansion strategy will ensure compliance with the risk reduction measures because Absorb GT1 BVS will be distributed in 2 phases, i.e., the Post-marketing Phase 1 covering 2-year follow-up of 250 patients enrolled in the use-results survey and the Post-marketing Phase 2 covering the period until the completion of 2-year follow-up of 2000 patients. In addition, the applicant plans to take appropriate measures, such as market withdrawal, if the results show no sufficient reduction in the incidence of ST and VLST or even a trend toward increased incidence. Thus, necessary safety measures have already been taken.

PMDA's view:
The submitted clinical study results showed a higher incidence of ST and VLST with Absorb GT1 BVS than XIENCE stents, suggesting a relationship between the events and the procedures, including selection of target lesions. While PCI is a commonly used surgical procedure in Japan, Absorb GT1 BVS is regarded as a novel medical device because of its resorbability. Absorb GT1 BVS also requires special cautions for its implantation compared with the implantation of conventional DESs. The applicant has claimed that the decreased incidence of ST, including VLST, can lead to a reduction in the incidence of TLF and MI, which tended to increase with Absorb GT1 BVS. The applicant's claim is understandable. The most critical safety measure is to reduce ST and VLST as far as practical. However, no sufficient evidence has been obtained on ST or VLST associated with Absorb GT1 BVS, and therefore the following post-marketing safety measures are necessary: (a) ensuring compliance with the currently optimal implantation procedures, (b) verifying that compliance with these procedures results in a decrease in the incidence of ST and VLST, and (c) taking further risk reduction measures based on accumulated evidence in Japan.

The applicant has planned to (a) require surgeons to participate in seminars and a doctor or marketing authorization holder's employee with full knowledge of Absorb GT1 BVS to be present during the surgery of the first 3 patients for each surgeon to ensure compliance with proper use of Absorb GT1 BVS in cooperation with related academic societies; (b) distribute Absorb GT1 BVS to limited medical institutions for a certain post-marketing period to ensure compliance with the appropriate implantation procedures, including selection of target vessels, and perform a use-results survey involving all patients treated with Absorb GT1 BVS to verify whether the incidence of acute/sub-acute ST is reduced by the above-mentioned measures before distribution of Absorb GT1 BVS is expanded in a stepwise manner; and (c) ensure that ST and VLST cases are reviewed at the Thrombosis Review Committee meetings in cooperation with related academic societies, analyze causes based on gathered information, and take risk reduction measures if necessary.

The above plans by presented by the applicant are acceptable. To accumulate more evidence on the incidence of VLST, the applicant has also planned to continue stepwise distribution of Absorb GT1 BVS

until a certain amount of information is accumulated, collect information on patients treated with Absorb GT1 BVS in cooperation with related academic societies, and take risk reduction measures, including market withdrawal, if necessary. PMDA accepted the applicant's explanation that the post-marketing safety could be ensured by strict risk control under this system and concluded that Conditions of Approval 1, 2, and 3 should be added. Conditions of Approval 4 should be added because it is important to review and analyze the long-term outcome for ST and VLST based on annual reports from the preceding clinical studies, thereby taking necessary risk reduction measures. PMDA asked the applicant to report the results of the planned investigator-initiated clinical research as necessary, and the applicant agreed.

6.B.4. Risk-benefit balance

As aforementioned, Absorb GT1 BVS is potentially associated with an increased risk for complications compare with conventional DESs. PMDA asked the applicant to explain the difference in benefits between Absorb GT1 BVS and conventional DESs.

The applicant's response:
Absorb GT1 BVS maintains the vessel lumen patency during the revascularization period to prevent re-stenosis as with conventional DESs, while it has a unique property by which the entire product is metabolized in the body after revascularization and eventually resorbs completely, except for the scaffold marker (platinum). The benefits specific to Absorb GT1 BVS will, therefore, be seen in the later period. Although no sufficient evidence on the long-term benefits of Absorb GT1 BVS has been obtained yet, Absorb GT1 BVS is expected to have some benefits compared with conventional DESs. The details of the benefits is described in sections below.

6.B.4.(1) Preservation of future re-intervention options

It is know that the history of PCI influences treatment policy and therapeutic procedures. Published literature has reported that sites for anastomosis were limited because of a previously implanted stent and that a very complicated surgical procedure was required for implantation of multiple metal stents (full metal jacket stent placement) when revascularization was required during bypass graft surgery.[29,30] Metal stents remaining in the body after the completion of their therapeutic role may complicate surgical procedures for future diseases and affect decision-making on treatment policy.[31]

On the other hand, Absorb GT1 BVS is free from the aforementioned problems with conventional metal stent implantation since the scaffold skeleton itself does not remain in the target blood vessel after a certain period. Re-intervention is expected to be easy after completion of the bioresorption of Absorb GT1 BVS. Absorb GT1 BVS is expected to provide a wider variety of options for future treatment than conventional metal stents, i.e., almost the same treatment options as those before the use of Absorb GT1 BVS.

6.B.4.(2) Physiological benefit (recovery of vascular function)

The 5-year follow-up of the ABSORB Cohort B study demonstrated the physiological benefits of Absorb GT1 BVS that have not been seen with DESs, namely recovery of vascular response after administration of nitroglycerin and the long-term maintenance of vessel lumen. Nitroglycerin is a non-

endothelium-dependent vasodilator. A clinical study in patients with coronary artery disease showed a lower incidence of cardiac events in a subgroup with vasodilatation after treatment with nitroglycerine than in a subgroup without vasodilatation.[32]

6.B.4.(3) Minimally invasive examination for follow-up

Study AVJ-301 demonstrated the superiority of BVS to XIENCE stents in stenosis assessment using MSCT at 13-month follow-up. This result suggests that noninvasive MSCT, instead of invasive coronary angiography, can be used to diagnose stenosis even after stent treatment.

According to the "Guidelines for Diagnostic Evaluation of Patients with Chronic Ischemic Heart Disease,"[33] coronary angiography is associated with a mortality of ≤0.2% and an incidence of major complications (cerebrovascular disorder, MI, and hemorrhage) of ≤0.5%.[34]

In addition, the "Guidelines for Noninvasive Diagnosis of Coronary Artery Lesions"[35] state that a new option of noninvasive diagnostic technique using CT is of great significance for patients.

6.B.4.(4) Treatment of patients with allergy to metals of conventional metal stents

Absorb GT1 BVS offers a treatment option to patients with hypersensitivity reaction to the raw materials of conventional metal stents or those with a history of allergy to metals.

Literature research on contact allergy in the general population demonstrated the median prevalence of allergy to nickel was approximately 8.6% (0.7% to 27.8%).[36] It has been reported in Japan and Germany that patients implanted with BMS who have allergy to nickel are prone to re-stenosis.[37,38] Biological factors, including hypersensitivity to metals, and mechanical/technical factors appear to be involved in the occurrence of ISR after metal stent implantation. ISR remains as a disadvantage of metal stents.[39]

Although the mechanism of neointimal proliferation leading to ISR is currently unknown,[37] extractables such as nickel and molybdenum released from metal stents may partly contribute to recurrent ISR.[40] The results of meta-analysis suggested their relationships, with a significant difference in odds ratio between the group with ISR and the group without ISR (an odds ratio of 2.25, 95% CI [1.43, 3.53]). A report concluded that stent implantation would aggravate prognosis in patients with allergy to metals.[41]

PMDA's view:

Absorb GT1 BVS has been developed to solve the problems with conventional DESs, which is an established standard intravascular treatment device for ischemic heart disease. As explained by the applicant, however, many of the promising benefits of Absorb GT1 BVS will be seen in the later phase. The submitted clinical study results only partially suggest the possibility of minimally invasive diagnostic examination for follow-up and the possibility of restoration of vascular function. No sufficient long-term data are available. However, given that Absorb GT1 BVS has been shown to fully resorb in the body, Absorb GT1 BVS may increase options for future treatment and address the risks associated with devices. Absorb GT1 BVS may also be one of the treatment options for patients with allergy to metals although its incidence is low. The effects of long-term benefits of Absorb GT1 BVS on clinical outcome, including the possibility of restoration of vascular function, cannot be assessed in

pre-marketing clinical studies. They should be investigated based on the long-term results of the ongoing clinical studies and evidence that will be accumulated in the post-marketing setting.

Study AVJ-301 and the ABSORB III study verified the non-inferiority of Absorb GT1 BVS to XIENCE stents, the second generation DES having stable results. Other clinical studies (ABSORB Cohort B, the ABSORB EXTEND, ABSORB II, and ABSORB China studies) also showed consistent results to those of Study AVJ-301 and the ABSORB III study. However, Absorb GT1 BVS was associated with a higher incidence of ST, including VLST, TLF, and TV-MI than XIENCE stents. The applicant has claimed that the risks of these events can be reduced by ensuring the proper use of Absorb GT1 BVS, including compliance with appropriate procedures, given the characteristics and high novelty of Absorb GT1 BVS. The applicant's claim is rational to a certain degree. The long-term benefit-risk balance of Absorb GT1 BVS is clinically acceptable provided that the applicant plans post-marketing safety measures and establishes an appropriate system in cooperation with related academic societies to ensure that the risk control is put in place. For these reasons and based on the comments from the Expert Discussion, PMDA has concluded that offering Absorb GT1 BVS to patients and healthcare professionals as one of the treatment options is of clinical significance. Considering that conventional DESs produce stable results as a standard intravascular treatment device for ischemic heart disease, however, the anticipated risks of Absorb GT1 BVS should also be communicated adequately to patients to be treated. PMDA instructed the applicant to include relevant precautions in the Instructions for Use and the applicant agreed. As described in Section "6.B.3. Post-marketing safety measures," guidance for proper use should be developed in cooperation with academic societies for surgeons. In addition, treating surgeons with sufficient knowledge and experience in relevant procedures should fully understand the efficacy and safety of Absorb GT1 BVS through skills training, etc. prior to use of this device. Thus, Condition of Approval 1 is appropriate. PMDA concluded that the underlined part should be added to the proposed intended use of Absorb GT1 BVS as shown below considering the intended use of conventional DESs.

Intended use or indication

Treatment of patients with <u>symptomatic</u> ischemic heart disease due to *de novo* coronary artery lesions (length ≤24 mm) with a reference vessel diameter of ≥2.5 mm and ≤3.75 mm

7. Plan for post-marketing surveillance etc. stipulated by Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

As described in Section "6.B.3. Post-marketing safety measures," PMDA has concluded that the safety of the bioresorbable scaffold that will be first introduced into Japan (particularly, the incidence of acute/sub-acute ST), and the appropriateness and adequacy of the proposed risk reduction measures should be confirmed in the use-results survey.

Table 52 presents the summary of the use-results survey of Absorb GT1 BVS. The duration of this survey is 7 years; 3 months for sales preparation, 1 year and 3 months for patient registration, 5 years for follow-up, and 6 months for analysis.

Table 52. Outline of use-results survey

Overall study	• 2000 patients (up to [redacted] medical institutions) • Primary objective: Verification of safety • Follow-up: 5 years • Priority endpoint: ST, including VLST • Other endpoints: ➢ General PCI's clinical endpoints ➢ Product malfunctions (e.g., difficulty in passing through an implanted BVS [positioning difficulty] and delivery)
Phase 1	• 250 patients (approximately [redacted] medical institutions) • Primary objective: Verification of the efficacy of skills training. This phase is intended to establish optimal training methods to increase the number of medical institutions participating in the post-marketing use-results survey. The outcome of the procedures will be assessed sequentially to provide early feedback to the participating medical institutions. For this purpose, no quantitative target to proceed to Phase 2 will be specified. The recommended procedures will be reviewed, as necessary, to achieve optimal acute-phase outcome. • Target lesion: Follow the Instructions for Use (similar to the criteria used in the Japanese clinical study). • Image-guided procedure using IVUS/OCT in all patients • Key endpoint 1: Exclusion of ultra-micro blood vessels • Key endpoint 2: Assessment of apposition and complete dilatation using IVUS/OCT (core lab analysis)
Phase 2	• Up to 2000 patients (up to [redacted] medical institutions) • Primary objective: Verification of safety • Target lesion: Follow the Instructions for Use. • Institutional standard procedure (image-guided procedure using IVUS/OCT recommended in the Instructions for Use) • Key endpoint: ST within 3 months In the ABSORB III study, 19 cases of definite/probable scaffold thrombosis (ST) occurred through 1 year. Since all of them occurred within 3 months (the longest time to onset, 78 days), interim safety analysis should be performed based on the incidence of ST through 3 months. Evaluation criteria: Incidence of ST (2000 patients, total of Phases 1 and 2) • ST occurring in ≤18 patients (0.9%): Commercial distribution of the product to other medical institutions will be started. • ST occurring in ≥19 patients: Causes of ST will be investigated to take appropriate measures. • When ST occurs in a patient, the medical institution must send all images of the patient to the core lab. Images of procedures performed in other patients will also be sent to the core lab for future analysis.

The applicant's explanation on the rationale for the sample size determined:

In the ABSORB III study, the incidence of ST in the target lesions with an RVD ≥2.25 mm was 0.9%. The incidence of ST in this use-results survey was estimated to be comparable to the above value (although compliance with the optimal procedure is expected to reduce the risk of ST, this survey may include more complicated lesions, thus offsetting the reduction). Table 53 presents the half width of the 95% CI for each sample size. [redacted]. The sample size for the use-results survey was, therefore, determined to be 2000.

Table 53. Sample size and half width of the 95% CI when the incidence of ST is 0.9%

	[redacted]		[redacted]	N = 2000	[redacted]		[redacted]
Incidence of thrombosis	0.9%		0.9%	0.9%	0.9%		0.9%
Half width of the 95% CI	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]

7.B. Outline of the review conducted by PMDA

PMDA accepted the applicant's explanation.

8. Contents of package insert, etc. specified in Paragraph 1, Article 63-2 of Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics regarding notification stipulated in said paragraph

8.A. Summary of the submitted data

A draft package insert was submitted in accordance with "Application for Medical Device Marketing Approval" (PFSB Notification No. 1120-5 dated November 20, 2014).

8.B. Outline of the review conducted by PMDA

On the basis of comments from the Expert Discussion, PMDA has concluded that there is currently no particular problem with the contents of package insert provided that the package insert advises necessary precautions, as described under "Outline of the review conducted by PMDA" of Section "6. Clinical data or alternative data accepted by the Minister of Health, Labour and Welfare."

IV. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

The new medical device application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the results of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

V. Overall Evaluation

Absorb GT1 BVS consists of a PLLA scaffold coated with everolimus and a delivery system. The clinical advantages of Absorb GT1 BVS eventually decomposing, resorbing, and disappearing is currently being investigated through long-term follow-up of the clinical studies and have not been demonstrated yet based on clear evidence. However, patients who do not want a device to be permanently placed in the body or those at a high risk for future additional treatment of a target lesion site may benefit from Absorb GT1 BVS, which eventually disappears from the body. On the basis of the discussion on issues shown below, PMDA has concluded that it is reasonable to approve Absorb GT1 BVS as one of the treatment options. The key issues discussed in the PMDA's review of Absorb GT1 BVS were (1) the efficacy and safety of Absorb GT1 BVS through 1 year, (2) the efficacy and safety of Absorb GT1 BVS at ≥1 year, and (3) post-marketing safety measures. Below are PMDA's conclusions based on comments from the Expert Discussion.

(1) Study AVJ-301 and the ABSORB III study were large-scale, controlled clinical studies that evaluated the efficacy and safety of Absorb GT1 BVS. Both studies successfully demonstrated the non-inferiority of Absorb GT1 BVS to XIENCE stents (which have been marketed for a long period

of time) in terms of the primary endpoint of TLF at 1 year. A series of clinical studies showed a trend toward a higher incidence of ST and MI in the BVS group than in the control group. MI often results from ST. To reduce these risks, the use of Absorb GT1 BVS should be avoided in ultra-micro blood vessels and full dilatation of the scaffold and good apposition of the struts should be achieved during device implantation, which will prevent the occurrence of ST within 1 year. The applicant should take necessary measures to ensure that only surgeons with sufficient knowledge and experience in procedures relevant to the use of Absorb GT1 BVS. This should be defined as Condition of Approval 1.

(2) In Study AVJ-301, 5 cases of VLST occurred in the BVS group, and the incidence of TLF at ≥1 year was higher in the BVS group than in the XIENCE group. The annual percent increase in the incidence of TLF was approximately 2% to 3% in the BVS group. Approximately half the increase in the incidence of TLF at ≥1 year was associated with VLST. The possible causes of VLST were inadequate dilatation, mal-apposition, and under-sized stent selection. The applicant has claimed that VLST events were clinically tolerable since improved procedures were expected to reduce the risk of VLST. PMDA accepted the applicant's claim. To reduce the risk of VLST, the applicant should take measures to ensure compliance with the proper implantation procedures, as with (1) above. Since no sufficient information on Absorb GT1 BVS-associated ST and VLST is available, the applicant should make every effort to identify ST and VLST cases and take further risk reduction measures as necessary. This should be defined as Condition of Approval 3. The applicant must submit annual reports of the clinical studies submitted to review their long-term results. This should be defined as Condition of Approval 4.

(3) The submitted clinical studies demonstrated a higher incidence of ST and VLST with Absorb GT1 BVS than conventional DESs. To reduce the risks, surgeons with sufficient experience in PCI should fully understand the characteristics and appropriate implantation procedures of Absorb GT1 BVS to ensure the proper use of the device. A system that ensures implementation of the aforementioned measures should be established. In addition, to verify that these measures can reduce the incidence of ST and VLST in Japan, the applicant should conduct a use-results survey involving all patients treated with commercial Absorb GT1 BVS to investigate long-term clinical outcomes, including ST, and take necessary measures (Condition of Approval 2). The applicant's post-approval marketing plan is reasonable, under which the distribution of Absorb GT1 BVS will be expanded in a stepwise manner while periodic analysis of long-term results of Absorb GT1 BVS will be performed for safe introduction into Japan.

Based on the above discussion, PMDA has concluded that Absorb GT1 BVS may be approved for the intended use shown below.

Intended Use

Treatment of patients with symptomatic ischemic heart disease due to *de novo* coronary artery lesions (length ≤24 mm) with a reference vessel diameter of ≥2.5 mm and ≤3.75 mm

Conditions of Approval

1. The applicant is required to take necessary measures in cooperation with related academic societies. For instance, guidance for proper use and skills training should be provided to surgeons to ensure that they fully understand the efficacy and safety of the product and have established knowledge and experience in relevant procedures.
2. The applicant is required to conduct a use-results survey involving all patients treated with the product in the post-marketing period until data from a certain number of patients have been gathered, to submit annual reports on the results of analyses of long-term outcomes to the Pharmaceuticals and Medical Devices Agency (PMDA), and to take appropriate measures as necessary.
3. The applicant is required to work with related academic societies to collect information on the occurrence of stent thrombosis for a certain period of time after approval and to take appropriate measures as necessary.
4. The applicant is required to submit, to PMDA, annual reports on the results of analyses of long-term outcome data from patients who participated in the submitted clinical studies and to take appropriate measures as necessary.

The product is not classified as a biological product or a specified biological product. The product should be designated as a medical device subject to the use-results survey. The duration of the use-results survey should be 7 years.

PMDA has concluded that the present application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

References

1. Nobuyoshi M, et al., Restenosis after successful percutaneous transluminal coronary angioplasty: Serial angiographic follow-up of 229 patients. *J. Am. Coll. Cardiol.* 1988;12:616-623.
2. Serruys P.W, et al., Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon. A quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months. *Circulation.* 1988;77:361-371.
3. Kimura T, et al., Remodeling of human coronary arteries undergoing coronary angioplasty or atherectomy. *Circulation.* 1997;96:475-483.
4. Pitt CG, et al., The degradation of poly (ε-caprolactone) *in vivo*. *J. Appl. Polym. Sci.* 1981;26(11):3779-3787.
5. Pitt CG, et al., The degradation of poly (DL-lactide), poly (ε-caprolactone), and their copolymers *in vivo*. *Biomaterials.* 1981;2(4):215-220.
6. Pitt CG, Gu ZW., Modification of the rates of chain cleavage of poly (e-caprolactone) and related polyesters in the solid state. *J. Controlled Release*. 1987;4(4):283-292.
7. Lyu S, et al., Kinetics and Time-Temperature Equivalence of Polymer Degradation. *Biomacromolecules.* 2007;8:2301-2310.
8. Perkins LEL., Preclinical Models of Restenosis and Their Application in the Evaluation of Drug-Eluting Stent Systems. *Veterinary Pathology*. 2010;47:58-76.
9. Wilson GJ, et al., Comparison of inflammatory response after implantation of sirolimus- and paclitaxel-eluting stents in porcine coronary arteries. *Circulation*. 2009;120(1-2):141-9.
10. Perkins LEL, et al., Inflammation in swine: host, device, or design? Society of Toxicologic Pathology. Chicago, IL, 2010: Abstract #61, Poster #25.
11. Schwartz RS, et al., Drug-Eluting Stents in Preclinical Studies: Updated Consensus Recommendations for Preclinical Evaluation. *Circ Cardiovasc Intervent.* 2008;1:143-153.
12. USDHHS C, CDER., Guidance for Industry and FDA Staff: General Considerations for Animal Studies for Cardiovascular Devices In: CDRH FaDA, ed. Rockville, MD; 2010.
13. Schoen FJ, et al., Biomaterial-associated calcification: Pathology, mechanisms, and strategies for prevention. *J. Biomed. Mater. Res.: Applied Biomaterials.* 1988;22(A1):11-36.
14. Lockwood NA, et al., In Vitro and In Vivo Characterization of Novel Biodegradable Polymers for Application as Drug-Eluting Stent Coatings. *Journal of Biomaterials Science*, *Polymer Edition*. 2010;21:529-552.
15. Vorpahl M, et al., The bioabsorption process: tissue and cellular mechanisms and outcomes. *Eurointerv.* 2010;5:F28-F35.
16. Brugaletta S, et al., Comparison between the first and second generation bioabsorbable vascular scaffolds: a six month virtual histology study. *Eurointerv.* 2011;6(9):1110-1116.

17. Brugaletta S, et al., Analysis of 1 year virtual histology changes in coronary plaque located behind the struts of the everolimus eluting bioresorbable vascular scaffold. *The International Journal of Cardiovascular Imaging (formerly Cardiac Imaging).* 2011;1-8.

18. Brugaletta S, et al., Head to head comparison of optical coherence tomography, intravascular ultrasound echogenicity and virtual histology for the detection of changes in polymeric struts over time: insights from the ABSORB trial. *EuroIntervention.* 2011;7(epub):1-7.

19. Serruys PW, et al., Dynamics of vessel wall changes following the implantation of the Absorb everolimus-eluting bioresorbable vascular scaffold: a multi-imaging modality study at 6, 12, 24 and 36 months. *EuroIntervention.* 2014;9:1271-1284.

20. Cutlip DE, et al., Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007 May 1;115(17):2344-51.

21. Naidu SS et al., *J Am Coll Cardiol Intv.* 2012;5:626-35.

22. Kereiakes DJ, et al., *J Am Coll Cardiol*. 2010;56:2084-9.

23. Palmerini T, et al., Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet*. 2012;379:1393-1402.

24. Kotani J. et al., Five-year outcomes of Cypher coronary stent: report from J-PMS Study. *Cardiovasc Interv and Ther*. 2012;27:63-71.

25. Shiomi H, et al., Long-Term Clinical Outcomes After Everolimus- and Sirolimus-Eluting Coronary Stent Implantation Final 3-Year Follow-Up of the Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial. *Circ Cardiovasc Interv*. 2014;7:343-354.

26. Patrick W. S, A Polylactide Bioresorbable Scaffold Eluting Everolimus for Treatment of Coronary Stenosis: 5-Year Follow-Up. *J Am Coll Cardiol*. 2016;67(7):766-776.

27. Taniwaki et al., *Circulation*. 2016;133:650-660.

28. Takahide Kodama, Tetsu Yamaguchi. Impact of IVUS-guided PCI and its present state in the world. *J Jpn Coron Assoc*. 2013;19:257-262.

29. Michael M., Does Percutaneous Coronary Intervention Compromise the Outcome of Subsequent Coronary Artery Bypass Grafting? *JACC*. 2009;2(8):765-766.

30. Tolga D, et al., Surgical Revascularization of the Left Anterior Descending Artery with Multiple Failed Overlapping Stents. *J Card Surg*. 2015;30(12):877-80.

31. Genichi Sakaguchi, et al., Impact of repeated percutaneous coronary intervention on long-term survival after subsequent coronary artery bypass surgery. *J Card Surg*. 2011;6:107.

32. Schachinger V, *Circulation*. 2000;101:1899.

33. Guidelines for Diagnostic Evaluation of Patients with Chronic Ischemic Heart Disease (2010 version).

34. Kennedy JW., Registry committee of the Society for Cardiac Angiography. Complications associated with cardiac catheterization and angiography. *Cathet Cardiovasc Diagn.* 1982;8:5-11.

35. Guidelines for Noninvasive Diagnosis of Coronary Artery Lesions (JCS 2009).

36. Thyssen, J.P., et al., The epidemiology of contact allergy in the general population - prevalence and main findings. *Contact Dermatitis*. 2007;57:287-299.

37. Saito, T., et al., Metal allergic reaction in chronic refractory in-stent restenosis. *Cardiovasc Revasc Med*. 2009;10(1):17-22.

38. Koster, R., et al., Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. *Lancet*. 2000;356(9245):1895-7.

39. Gray, W.A. and J.F. Granada, Drug-coated balloons for the prevention of vascular restenosis. *Circulation*. 2010;121(24):2672-80.

40. Iijima, R., et al., The impact of metallic allergy on stent implantation: metal allergy and recurrence of in-stent restenosis. *Int J Cardiol*. 2005;104(3):319-25.

41. Gong, Z., et al., Stent implantation in patients with metal allergy: a systemic review and metaanalysis. *Coron Artery Dis*. 2013;24(8):684-9.