October 7, 2024

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

Report on the Deliberation Results

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Aortic stent graft
Brand Name	GORE EXCLUDER Thoracoabdominal Branch Endoprosthesis
Applicant	W. L. Gore & Associates G.K.
Date of Application	November 28, 2023 (Application for marketing approval)

Results of Deliberation

In its meeting held on October 7, 2024, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Council.

The product should be approved with designation as a medical device subject to a use-results survey. The product is not classified as a biological product or a specified biological product.

The use-results survey period should be 9 years. The product should be approved with the following conditions.

Approval Conditions

1. The applicant is required to take necessary measures, such as dissemination of the guidelines for proper use of the product prepared in cooperation with relevant academic societies and delivery of seminars, to ensure that physicians and medical team members with adequate knowledge and experience in the treatment of thoracoabdominal aortic aneurysms and pararenal abdominal aortic aneurysms acquire full skills of the product usage and knowledge in complications associated with the procedure and identify patients eligible for the treatment and that the physicians use the product at medical institutions with an established system for the treatment.
2. The applicant is required to conduct a use-results survey involving all patients treated with the product in the post-marketing setting until data from a specified number of patients have been accrued, thereby reporting the survey results to the Pharmaceuticals and Medical Devices Agency and taking other appropriate measures as necessary.

3. The applicant is required to submit annual reports on the results of analysis of the long-term outcome of the patients treated in the clinical study included in this regulatory submission to the Pharmaceuticals and Medical Devices Agency and to take appropriate measures as necessary.

Review Report

September 18, 2024
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	Aortic stent graft
Brand Name	GORE EXCLUDER Thoracoabdominal Branch Endoprosthesis
Applicant	W. L. Gore & Associates G.K.
Date of Application	November 28, 2023
Reviewing Office	Office of Medical Devices II

Review Results

September 18, 2024

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Aortic stent graft
Brand Name	GORE EXCLUDER Thoracoabdominal Branch Endoprosthesis
Applicant	W. L. Gore & Associates G.K.
Date of Application	November 28, 2023

Results of Review

The GORE EXCLUDER Thoracoabdominal Branch Endoprosthesis (hereinafter referred to as the TAMBE Device) is intended for use in the endovascular treatment of patients with thoracoabdominal aortic aneurysm (TAAA) or pararenal abdominal aortic aneurysm (PAAA). The TAMBE Device consists of a stent graft and a delivery catheter. The stent graft of the TAMBE Device has 4 portals to maintain the blood flow to the celiac artery, superior mesenteric artery, and bilateral renal arteries. Existing approved stent grafts are used as the Branch Components (BCs), which are connected to these portals, the Distal Bifurcated Component (DBC), which is placed distal to the TAMBE Device, and other components (hereinafter referred to as the TAMBE System).

The applicant submitted non-clinical data supporting the physicochemical properties, biological safety, and stability and durability of the TAMBE Device. There was no particular problem in the data submitted.

For the clinical evaluation of the TAMBE Device, the applicant submitted the results of a multicenter clinical study conducted in the US and the UK to evaluate the safety and efficacy of the TAMBE System in the treatment of TAAA and PAAA (hereinafter referred to as the clinical study). The clinical study consisted of the Primary Study Arm including patients with Type IV TAAA or PAAA, and the Secondary Study Arm including patients with Type I to III TAAA. The clinical study used 2 independent co-primary endpoints. It was expected to be challenging to achieve the sample size necessary to test a hypothesis in the Secondary Study Arm. In this arm, therefore, data on the same endpoints as those for the Primary Study Arm were collected and evaluated with a focus on potential additional risks of the TAMBE Device in combination with the thoracic component (TC), which is intended for use to extend the proximal end of the TAMBE Device.

The percentage of subjects who achieved “uncomplicated technical success and procedural safety” (Primary Endpoint 1) in the Primary Study Arm was 77.5% (79 of 102 subjects; 95% confidence interval [CI], 69.6%-84.1%). The lower limit of the confidence interval did not meet a performance goal of 80%. The percentage of subjects who experienced freedom from “clinically significant reintervention and lesion-related mortality” (Primary Endpoint 2) was 70.6% (60 of 85 subjects; 95%

CI, 61.4%-78.7%). The lower limit of the confidence interval did not meet a performance goal of 68%. The possible reasons for the failures are the following: The criteria for implantation of additional devices in stent grafting with the TAMBE Device were inappropriate, and the definition of clinically significant reintervention was different from that in literature used to determine the performance goal. A reanalysis performed after these issues were addressed showed that the performance goals were met, without perioperative death, and aneurysm rupture or aneurysm-related death through 12 months postoperative. In view of the results, the clinical study demonstrated the efficacy and safety of the TAMBE System as an endovascular device in the treatment of PAAA and Type IV TAAA. In the clinical study, however, BC occlusion occurred in 14 of 95 subjects (14.7%) through 12 months postoperative or 19 of 102 subjects (18.6%) through the end of the follow-up period. Not a few subjects experienced serious outcomes including death from intestinal ischemia or renal failure, renal function deterioration, and dialysis.

In the Secondary Study Arm, the percentage of subjects who achieved Primary Endpoint 1 was 92.0% (23 of 25 subjects) and the percentage of subjects who experienced freedom from Primary Endpoint 2 was 58.8% (10 of 17 subjects). Endoleaks requiring reintervention tended to more frequently occurred in the Secondary Study Arm than in the Primary Study Arm. These endoleaks did not lead to clinically significant events such as aneurysm enlargement. No events (including endoleak) related to TC implantation, which was required only in the Secondary Study Arm, were reported. BC occlusions occurred in 2 of 20 subjects (10.0%) through 12 months postoperative. Both cases resulted in renal function deterioration. Although the sample size was limited, the clinical study showed no perioperative death, or aneurysm rupture or aneurysm-related death through 12 months postoperative, suggesting the efficacy and safety of the TAMBE Device in the treatment of Type I to III TAAA.

The 30-day mortality for surgical repair in Japan was reportedly approximately 7.5% and 2.0% in the treatment of TAAA and PAAA, respectively. The data suggest the clinical need for the TAMBE Device that was not associated with death in 30 days postoperative. However, the TAMBE System was associated with a relatively high incidence of BC occlusions. The risks of serious complications of BC occlusion, including death, intestinal ischemia, renal disorder, and dialysis, are currently unavoidable. Surgical repair is associated with a low risk of branch vessel occlusion. There is only limited clinical experience with use of the TAMBE System in the treatment of TAAA and PAAA. From the viewpoint of the risk-benefit balance and taking into consideration the comments from the Expert Discussion, PMDA concluded that the TAMBE Device should be indicated for patients with TAAA or PAAA who are not eligible for surgical repair.

The TAMBE Device will be the first branch stent graft system in Japan, which is intended for use in the treatment of TAAA and PAAA. In order to implement the effective and safe use of the TAMBE System in Japan, physicians and medical team members with adequate knowledge and experience in the treatment of the target diseases should acquire the necessary knowledge and skills regarding the TAMBE System and relevant procedures through training sessions and other learning opportunities and identify patients eligible for the treatment taking into account the risks for the TAMBE Device implantation versus surgical repair. Since perioperative or postoperative complications need immediate

medical interventions including surgery, the TAMBE Device implantation should be performed at medical institutions with an established system for emergencies.

In addition, the applicant should collect information on the relevant procedures and skills required for the use of the TAMBE System, adverse events including branch vessel occlusion, long-term outcomes, etc. through a use-results survey, and take additional risk mitigation measures as necessary. Since there is only limited data on the long-term outcomes of the TAMBE Device implantation, including overseas data, the applicant is also required to annually report follow-up results of the submitted clinical study so as to assess the long-term outcomes of the treatment.

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

Intended Use

The GORE EXCLUDER Thoracoabdominal Branch Endoprosthesis is indicated for high-surgical risk patients with thoracoabdominal aortic aneurysms or patients with pararenal aortic aneurysms who meet the anatomical requirements, and used with designated stent grafts whose efficacy and safety have been shown when used in combination with the GORE EXCLUDER Thoracoabdominal Branch Endoprosthesis.

Approval Conditions

1. The applicant is required to take necessary measures, such as dissemination of the guidelines for proper use of the product prepared in cooperation with relevant academic societies and delivery of seminars, to ensure that physicians and medical team members with adequate knowledge and experience in the treatment of thoracoabdominal aortic aneurysms and pararenal abdominal aortic aneurysms acquire full skills of the product usage and knowledge in complications associated with the procedure and identify eligible patients for the treatment and that the physicians use the product at medical institutions with an established system for the treatment.
2. The applicant is required to conduct a use-results survey involving all patients treated with the product in the post-marketing setting until data from a specified number of patients have been accrued, thereby reporting the survey results to the Pharmaceuticals and Medical Devices Agency and taking other appropriate measures as necessary.
3. The applicant is required to submit annual reports on the results of analysis of the long-term outcome of the patients treated in the clinical study included in this regulatory submission to the Pharmaceuticals and Medical Devices Agency and to take appropriate measures as necessary.

Review Report

September 18, 2024

Product for Review

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Aortic stent graft
Brand Name	GORE EXCLUDER Thoracoabdominal Branch Endoprosthesis
Applicant	W. L. Gore & Associates G.K.
Date of Application	November 28, 2023 (Application for marketing approval)
Proposed Intended Use	The GORE EXCLUDER Thoracoabdominal Branch Endoprosthesis is indicated for patients with thoracoabdominal aortic aneurysms or high-surgical risk patients with pararenal aortic aneurysms, and used with designated stent grafts* whose safety and efficacy has been shown when used in combination with the GORE EXCLUDER Thoracoabdominal Branch Endoprosthesis. *Refer to the Directions for use, etc.

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List of Abbreviations

AC	Aortic Component
BC	Branch Component
BMI	Body Mass Index
eGFR	estimated Glomerular Filtration Rate
EXC-AE	EXCLUDER-Aortic Extender
CEC	Clinical Events Committee
CLC	Contralateral Leg Component
CT	Computed Tomography
DBC	Distal Bifurcated Component
DUS	Duplex Ultrasound Scanning
EVAR	EndoVascular Aortic Repair
MRI	Magnetic Resonance Imaging
PAAA	Pararenal Abdominal Aortic Aneurysm
RGT	Removable Guidewire Tube
SAE	Serious Adverse Event
SMA	Superior Mesenteric Artery
SVS	Society for Vascular Surgery
TAAA	Thoraco-Abdominal Aortic Aneurysm
TC	Thoracic Component
TEVAR	Thoracic Endovascular Aortic Repair

I. Product Overview

The GORE EXCLUDER Thoracoabdominal Branch Endoprosthesis (hereinafter referred to as the TAMBE Device) is intended for use in the endovascular treatment of patients with thoracoabdominal aortic aneurysm (TAAA) or pararenal abdominal aortic aneurysm (PAAA). The TAMBE Device consists of a stent graft and a delivery catheter. The stent graft of the TAMBE Device (Aortic Component [AC], Figure 1) has 4 portals to maintain the blood flow to the celiac artery, superior mesenteric artery, and bilateral renal arteries. The company's approved device Gore stent graft "Gore Viabahn VBX Balloon Expandable Endoprosthesis" (Approval number, 22900BZX00309000) is used as a Branch Component (BC), which is connected to these portals. The company's approved device Gore stent grafts "EXCLUDER Bifurcated Endoprosthesis" (Approval number, 21900BZY00011000) are used as the Distal Bifurcated Component (DBC) and Contralateral Leg Component (CLC), which are placed distal to the TAMBE Device (hereinafter referred to as the TAMBE System). In addition to these components, the following optional components may be used as necessary depending on the conditions of the target lesion and the placement of TAMBE Device: "Gore CTAG Thoracic Endoprosthesis" (Approval number, 22500BZX00427000) as the Thoracic Component (TC) that is used to extend the proximal end of the TAMBE Device, and the Aorta Extender of "EXCLUDER Bifurcated Endoprosthesis" as the EXCLUDER-Aortic Extender (EXC-AE) that is to strengthen the junction of the AC and the DBC (Figure 2 and Table 1).

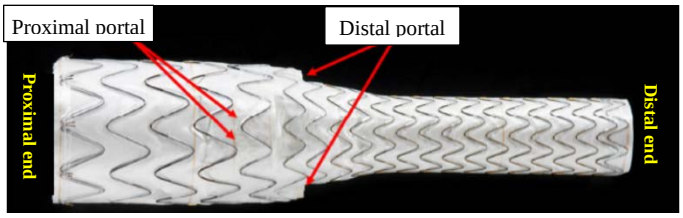

Figure 1. Appearance of the TAMBE Device (Aortic Component [AC])

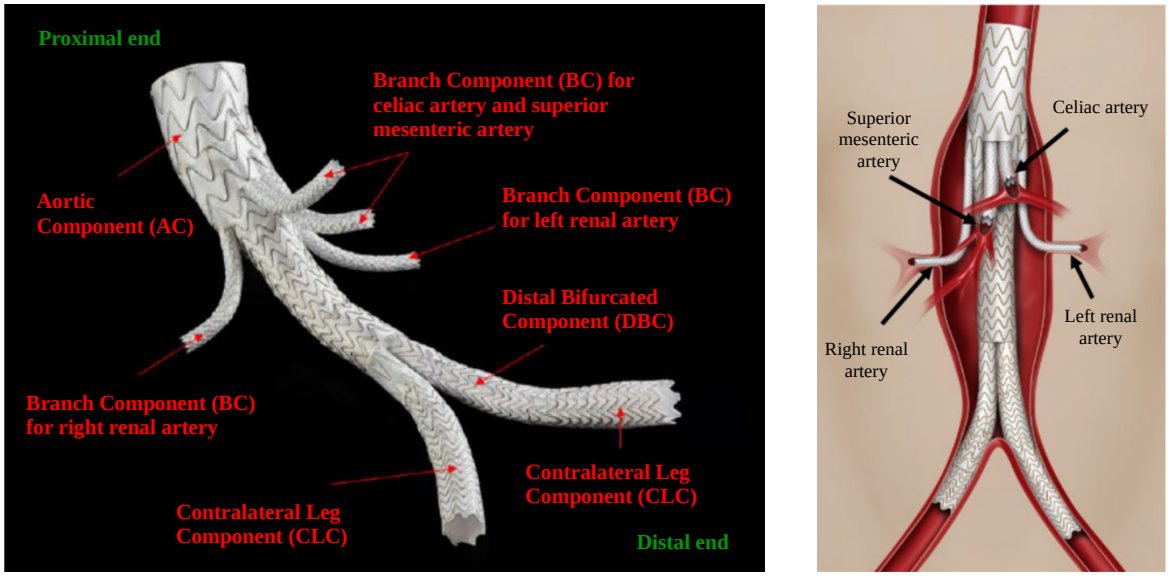

Figure 2. Appearance of the TAMBE System and illustration of the TAMBE Device implantation

Table 1. Components of the TAMBE System

Component	Abbreviation	Location for implantation	Brand name and name of constituent part
Aortic Component	AC	Aorta	GORE EXCLUDER Thoracoabdominal Branch Endoprosthesis
Branch Component	BC	Celiac artery Superior mesenteric artery Left and right renal arteries	Gore Viabahn VBX Balloon Expandable Endoprosthesis
Distal Bifurcated Component	DBC	Aorta to celiac artery	EXCLUDER Bifurcated Endoprosthesis • Iliac Branch Component
Contralateral Leg Component	CLC	Celiac artery	EXCLUDER Bifurcated Endoprosthesis • Contralateral Leg • Iliac Extender
DBC Extender Component[1]	EXC-AE	Within a stent graft (between AC and DBC)	EXCLUDER Bifurcated Endoprosthesis • Aorta Extender
Thoracic Component[2]	TC	Aorta	Gore CTAG Thoracic Endoprosthesis

[1] This component is placed in the junction of the AC and DBC as necessary.
[2] This component is placed proximal to the AC as necessary.

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

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

The expert advisors present during the Expert Discussion on the TAMBE Device declared that they did not fall under the Item 5 of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. Origin or History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

For the treatment of patients with thoraco-abdominal aortic aneurysm (TAAA) or pararenal abdominal aortic aneurysm (PAAA), who are at risks of aortic rupture, a conservative treatment option (medical therapy) or invasive treatment option (surgical repair or endovascular therapy) is considered depending on their aneurysm size, enlargement rate, etc. The Japanese guidelines recommend an invasive option for the treatment of TAAA with an aneurysm size of ≥60 mm or an aneurysm enlargement rate of ≥5 mm/6 months, or for the treatment of abdominal aortic aneurysms including PAAA with an aneurysm size of ≥55 mm or an aneurysm enlargement rate of ≥5 mm/6 months. Patients who do not meet these criteria are treated by conservative therapy to prevent aneurysm enlargement and the progression of comorbidities.[1]

Of invasive treatment options, surgical repair is selected for patients at a low to moderate surgical risk.[1] TAAA involves a large portion of the aneurysm and requires reconstruction of visceral vessels. Since it is highly invasive and technically-challenging, surgical repair for the treatment of TAAA is reportedly associated with a high incidence of perioperative complications (30-day mortality [7.5%], cerebrovascular accident [6%], renal failure [18.5%], pneumonia [9.6%], paraplegia [9%], including dissociation and rupture).[2] The surgical success rate in the treatment of PAAA, which requires interruption of the blood flow to the visceral vessels, also reportedly tends to be lower than that in the treatment of infrarenal abdominal aortic aneurysms (a 30-day mortality of 0.8% and an in-hospital

mortality of 1.2% in patients requiring no interruption/reconstruction of the renal artery versus a 30-day mortality of 2.0% and an in-hospital mortality of 3.8% in patients requiring interruption/reconstruction of the renal artery).[3]

While stent grafting has widely been used for the treatment of thoracic or abdominal aortic aneurysms, no approved device is available for stent grafting to treat TAAA or PAAA. The usefulness of the endovascular treatment of TAAA or PAAA in comparison with surgical repair is unclear. However, endovascular treatment is considered in patients in whom surgical repair may be difficult, such as high surgical risk patients. Endovascular therapies include a hybrid therapy that involves laparotomy and surgical bypass of a visceral vessel for stent grafting, snorkel/chimney method that places a stent graft for the visceral vessel in parallel to the aortic stent graft, and stent grafting using physician-modified branch or fenestrated stent graft. These endovascular treatments are performed at limited medical institutions in Japan. Although only limited treatment outcomes are available for the treatment with physician-modified stent grafts in Japan, the in-hospital mortality is 8.5% for TAAA and 3.2% for PAAA, and the percentage of subjects who experienced 3-year freedom from aneurysm-related death is 82.7% for TAAA and 96.8% for PAAA.[4] These data suggest the usefulness of endovascular therapies for the treatment of TAAA and PAAA.

The current standard therapy for TAAA and PAAA is surgical repair. However, surgical repair is invasive and technically-challenging, and is associated with a high perioperative mortality and a high incidence of serious complications. These are the challenges of surgical repair. There is a growing clinical need for endovascular treatment for patients who are not eligible for surgical repair because of these risks or patients who are eligible for surgical repair but prefer a less invasive therapy. Currently, no approved device for stent grafting, which is one of the standard therapies for thoracic or abdominal aortic aneurysms, is available for the treatment of TAAA or PAAA. This stent graft system (TAMBE System), consisting of the TAMBE Device and the approved multiple components of Gore, was developed as a less-invasive endovascular device intended to interrupt the blood flow to TAAA and PAAA in order to prevent them from expanding and rupturing while maintaining the blood flow to the visceral vessels and the lower limbs.

1.A.(2) Use in foreign countries

The TAMBE Device was approved in January 2024 in the US. Table 2 presents the intended use and the number of units used.

Table 2. Intended use and the number of patients using TAMBE Device overseas (as of June 30, 2024)

Country	Intended use or indication	Number of patients using TAMBE Device
US	The GORE EXCLUDER Thoracoabdominal Branch Endoprosthesis is indicated for endovascular repair in patients with thoracoabdominal aortic aneurysms and high-surgical risk patients with pararenal aortic aneurysms who have appropriate aortic anatomy as described below: 1. Adequate iliac/femoral artery access and brachial/axillary artery access 2. Proximal (supraceliac) aortic neck treatment diameter range over 2 cm seal zone of 22 to 34 mm for aneurysms extending up to ≤6.5 cm above the origin of the most proximal branch vessel 3. Aortic neck angle ≤60° at the Aortic Component proximal seal zone 4. Iliac artery treatment diameter range of 8 to 25 mm and iliac artery seal zone length of ≥10 mm 5. Renal artery seal zone diameters between 4.0 and 10.0 mm 6. Celiac and superior mesenteric artery seal zone diameters between 5.0 and 12.0 mm 7. ≥15 mm seal zone length in renal arteries, superior mesenteric artery, and celiac artery 8. Visceral segment of aorta (3 cm proximal through 9.5 cm distal to the most proximal visceral artery) ≥20 mm in diameter	■ patients

1.A.(3) Malfunctions and adverse events in foreign countries

Table 3 presents incidences of malfunctions and adverse events reported for the TAMBE Device in foreign countries. Table 4 presents incidences of malfunctions and adverse events reported for the EXCLUDER Bifurcated Endoprosthesis, which is used in combination with the TAMBE Device. No adverse event has been reported for the Gore Viabahn VBX Balloon Expandable Endoprosthesis.

Table 3. Incidences of malfunctions and adverse events reported for the TAMBE Device in foreign countries

Malfunctions and adverse events	Number of events	Incidence (%)
Postoperative placement of an additional stent/stent graft	■	5.88
Perioperative aortic dissection	■	2.94
Postoperative dissection of aortic arch branch vessel	■	2.94
Difficult or impossible cannulation of the target branch vessel	■	2.94
Perioperative embolism	■	2.94
Postoperative drain placement in the spine	■	2.94
Paraparesis	■	2.94

Table 4. Incidences of malfunctions and adverse events reported for the concomitant medical device (EXCLUDER Bifurcated Endoprosthesis) in foreign countries

Malfunctions and adverse events	Number of events	Incidence (%)[1]
Paraparesis[2]	■	2.94
Postoperative drain placement in the spine[2]	■	2.94
Migration to the distal end of the stent graft during its deployment (>5 mm)	■	2.94
Perioperative placement of an additional stent/stent graft	■	2.94

[1] Incidence based on the number of patients treated
[2] The same event as that occurring with the TAMBE Device

1.B Outline of the review conducted by PMDA

The above data, including the incidences, are discussed later in Section 6.

2. Setting of Specifications

2.(1) Performance and safety specifications

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

The proposed performance and safety specifications for the stent graft of the TAMBE Device were acute migration resistance, radial force, magnetic resonance imaging (MRI) safety, stent graft wall leakage, bend radius, durability, corrosion resistance, and pressure drop.

The proposed performance and safety specifications for the delivery catheter were catheter bond strength, catheter leak, and catheter angular rotation to failure.

The proposed performance and safety specifications for the whole stent graft system were guidewire compatibility, pushability and trackability, torqueability, deployment force, deployment mechanism to line tensile strength, tip bond strength, [redacted] bond strength, deployment reliability, radiopacity, biological safety, ethylene oxide sterilization residuals, and bacterial endotoxins.

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

PMDA requested the applicant to establish specifications of the longitudinal tensile strength and graft rupture strength of the stent graft because these are key properties to assure the performance of the TAMBE Device.

The applicant submitted the test results of longitudinal tensile strength and graft rupture strength, and explained that these tests would be included in the specifications.

PMDA reviewed the data and information about the proposed specifications and concluded that there was no particular problem in the proposed tests and limits.

2.(2) Physicochemical properties

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

To support the physicochemical properties of the stent graft of the TAMBE Device, the applicant submitted the test results of radial force, bend radius, modular component separation force, MRI, longitudinal tensile strength, and graft rupture strength.

To support the physicochemical properties of the delivery catheter, the applicant submitted the test results of delivery system bond strength (catheter), delivery system bond strength (between catheter and handle; [1] tensile strength, [2] torque strength), delivery system bond strength [redacted], and delivery catheter angular rotation.

To support the physicochemical properties of the whole stent graft system, the applicant submitted the test results of [redacted], deployment, radiopacity, deployment in a simulating use environment, and bacterial endotoxins.

The test results met the predefined acceptance criteria. The MRI compatibility test showed that the TAMBE Device was MRI compatible in conditioned environments. The MRI conditions are included in the instructions for use.

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

PMDA reviewed the data supporting the physicochemical properties and concluded that there was no particular problem.

2.(3) Biological safety

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

The stent graft of the TAMBE Device uses the same materials and sterilization method as those for the company's approved device Gore CTAG Thoracic Endoprosthesis and EXCLUDER Bifurcated Endoprosthesis. The manufacturing process, site of use, duration of use, shape, and physical properties of the TAMBE stent graft are also similar to those of the above approved devices. For these reasons, no biological safety test of the TAMBE stent graft was conducted.

To support the biological safety of the delivery catheter, the applicant submitted the test results of cytotoxicity, sensitization potential, irritation/intradermal reaction, acute systemic toxicity, pyrogenicity, and blood compatibility. There was no problematic finding in any of the test results submitted.

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

PMDA reviewed the data supporting the biological safety and concluded that there was no particular problem.

2.(4) Stability and durability

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

The applicant omitted test results supporting the stability of the TAMBE Device and submitted a self-declaration stating that its shelf-life was determined based on the results of the necessary stability study in accordance with the "Handling of stability studies related to the determination of the shelf life in the application for marketing approval (certifications) of medical devices (in Japanese)" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012).

To support the durability of the stent graft, the applicant submitted the test results of the pulsatile fatigue of AC [redacted], fatigue of AC [redacted], pulsatile fatigue and respiratory-induced bend fatigue of [redacted], and longitudinal compression fatigue of [redacted].

The pulsatile fatigue test of AC [redacted], where the AC was deployed in a mock blood vessel with the [redacted] target vascular diameter and subjected to accelerated pulsatile loads of 380 million cycles corresponding to 10 years, showed stent loosening, graft adhesive tape wear, and partial stent separation in the proximal area of [redacted] of [redacted] samples. All of these defects were mild in severity and did not damage the device function. The fatigue test of AC [redacted], where the AC was

deployed in a mock blood vessel and subjected to pulsatile fatigue loads of 380 million cycles, showed the wear and partial peeling of the adhesive tape at the top of [redacted]. These defects were considered acceptable because the area peeled was small and [redacted] maintained its function. The pulsatile fatigue test of [redacted], where [redacted] was placed in a mock blood vessel with an inner diameter [redacted] based on finite element analysis and subjected to pulsatile fatigue loads of 380 million cycles, showed a total of [redacted] stent wire fractures ([redacted] and [redacted]). No case of fracture resulted in graft damage, penetration into the graft lumen, or stent graft occlusion. These fractures did not damage device function. The respiratory-induced bend fatigue test of [redacted], where [redacted] was placed in a mock blood vessel and subjected to bend fatigue loads of [redacted] cycles corresponding to 10 years of breathing, showed [redacted] stent wire fractures in the BC. No graft damage, penetration into the graft lumen, or stent graft occlusion was observed. These fractures did not damage device function. The longitudinal compression fatigue test of [redacted], where [redacted] was placed in a mock blood vessel and added with longitudinal compression loads of [redacted] cycles corresponding to 10 years of breathing at [redacted] of [redacted]% based on analysis of [redacted] data of the visceral vessels, showed holes in some sample grafts. These holes were considered acceptable because their sizes and locations would not damage device function.

[redacted]

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

PMDA concluded that the defects shown in the durability tests were minimal and did not affect the structure or function of the whole stent graft, and were therefore acceptable. PMDA reviewed the data supporting the stability and durability, and concluded that there was no particular problem.

The stent wire fractures, along with defects reported in the clinical study, are assessed later in Section 6.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that the TAMBE Device meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as “the Essential Principles”) (MHLW Public Notice No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the TAMBE Device to the Essential Principles.

(1) PMDA's view on the conformity of the TAMBE Device to Article 1, which stipulates preconditions, etc. for designing medical devices (particularly requirements for users, such as the expected level of technical knowledge and experience, and the expected level of education and training for users):

As described later in Sections "6.B Outline of the review conducted by PMDA," the identification of eligible patients, user training, and adherence to the guidelines for proper use prepared in cooperation with relevant academic societies are important to maintain the risk-benefit balance of the TAMBE Device. To this end, approval conditions should be imposed so that necessary measures are taken.

(2) PMDA's view on the conformity of the TAMBE Device to Article 2, which stipulates requirements for risk management throughout the product life cycle of medical devices:

As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," the efficacy and safety of the TAMBE Device during clinical use in Japan must be evaluated because of the lack of clinical efficacy or safety data of the TAMBE Device in Japan. In addition, additional risk mitigation measures must be taken as necessary. PMDA instructed the applicant to conduct a use-results survey.

(3) PMDA's view on the conformity of the TAMBE Device to Article 3, which stipulates requirements for the performance and functions of medical devices, and to Article 6, which stipulates the efficacy of medical devices:

As described later in Sections "6.B Outline of the review conducted by PMDA," the clinical study of the TAMBE Device confirmed that the identification of eligible patients by physicians with adequate knowledge and experience in the implantation procedures of the TAMBE Device would ensure the effective and safe use of the TAMBE Device. The TAMBE Device properly conforms to Articles 3 and 6.

(4) PMDA's view on the conformity of the TAMBE Device to Article 17, which stipulates requirements for publicizing information including precautions or the communication of information to users via instructions for use, etc. (the Information for Precautions, etc.):

As described later in Sections "6.B Outline of the review conducted by PMDA," physicians with adequate knowledge and experience in diagnosis and treatment of TAAA and PAAA must identify eligible patients and understand the characteristics of the TAMBE Device before using it to maintain the risk-benefit balance of the TAMBE Device. To this end, the applicant should provide relevant information to the physicians through the Information for Precautions, etc., the guidelines for proper use, training, and by other means.

PMDA concluded that there was no particular problem with the conformity of the TAMBE Device to the Essential Principles.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted the document summarizing the risk management system and its activities implemented for the TAMBE Device in accordance with ISO 14971:2019 “Medical devices – Application of risk management to medical devices.”

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the document on risk management taking into account the discussion presented earlier in Section “3.B Outline of the review conducted by PMDA” and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on the sterilization method for the TAMBE Device (sterilization validation and ethylene oxide sterilization residuals). The applicant also submitted the data on the in-process tests of the TAMBE Device.

5.B Outline of the review conducted by PMDA

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

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

6.A Summary of the data submitted

The applicant submitted the results of a multicenter clinical study conducted in the US and the UK to evaluate the safety and efficacy of the TAMBE System in the treatment of TAAA and PAAA (hereinafter referred to as the clinical study).

6.A.(1) Study design

The clinical study was a multicenter, single-arm clinical study conducted to evaluate the safety and efficacy of the TAMBE System in the treatment of TAAA and PAAA. The study was conducted at 42 study sites in the US and 2 study sites in the UK and included patients with TAAA or PAAA who had anatomies suitable for use of the TAMBE Device and were expected to benefit from endovascular approach when compared to open surgical repair as deemed by the study investigator. Taking into consideration the TAAA categories (Crawford classification) established by the Society of Vascular Surgery (SVS)[5,6], the definition of PAAA shown in a published literature report,[7] and anatomical requirements for the TAMBE Device, TAAA and PAAA were classified as presented in Table 5 and Figure 3. Patients with Type IV TAAA or PAAA were included in the Primary Study Arm in the clinical study. Patients with Type I to III TAAA, who are high-risk patients with extensive aneurysms and require additional placement of the Thoracic Component (TC), were included in the Secondary Study Arm.

Table 5. Classification of TAAA and PAAA in the clinical study

Classification		Definition	Study arm (device used)
TAAA	Type I	It begins in the proximal half of the descending thoracic aorta (equivalent to "above T6 intervertebral disc space"), involves the remaining of the descending thoracic aorta, and transcends the diaphragmatic boundary, involving the upper abdominal aorta without extending below the renal arteries.	Secondary Study Arm (TAMBE System + Thoracic Component)
	Type II	It begins in the proximal half of the descending thoracic aorta (equivalent to "above T6 intervertebral disc space"), involves most or all of the descending thoracic aorta and most or all of the abdominal aorta, and extends below the renal arteries.	
	Type III	It involves the distal half of the descending thoracic aorta (equivalent to "below T6 intervertebral disc space") with aneurysm enlargement beyond 65 mm proximal to the celiac artery and involves a variety of segments of the abdominal aorta.	
	Type IV	It includes most or all of the entire abdominal aorta (including the renal arteries) with aneurysm enlargement as far as 65 mm proximal to the celiac artery.	Primary Study Arm (TAMBE System)
PAAA		No normal neck between the proximal end of aneurysm and the renal artery(ies)	

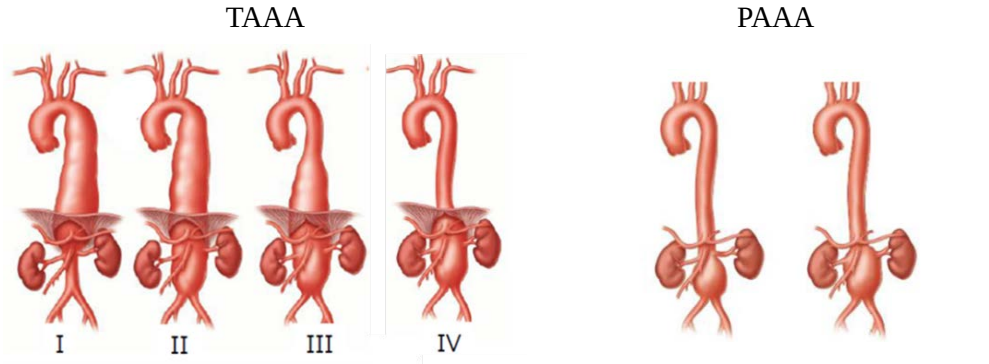

Figure 3. Classification of TAAA and PAAA

Table 6 presents the outline of the clinical study. The primary endpoints were "uncomplicated technical success and procedural safety" (Primary Endpoint 1) and "clinically significant reintervention and lesion-related mortality" (Primary Endpoint 2). The performance goal of Primary Endpoint 1 was 80% as determined based on the incidence of safety events estimated from literature data on surgical repair of TAAA and PAAA (15%), the technical failure rate estimated from the results of clinical studies of aortic stent grafts conducted by W. L. Gore & Associates, Inc. (3%), and uncertainty and proficiency associated with the novelty of the TAMBE Device including the procedures (2%). The performance goal of Primary Endpoint 2 was 68% as determined from the incidence of reinterventions in the endovascular treatment of TAAA and PAAA reported in published literature (15%), the incidence of events in relation to the learning curve of the procedure (5%), and the margin for uncertainty (12%).

Hypothesis testing was performed in the Primary Study Arm. In the Secondary Study Arm, the same endpoints as those for the Primary Study Arm were collected and evaluated with a focus on potential additional risks of the concomitant use of the TC because the target patient population to be enrolled in the Secondary Study Arm is small and it was expected to be challenging to achieve the sample size necessary to perform hypothesis testing in this arm.

Table 6. Outline of the clinical study

Item	Outline
Study objective	To evaluate the safety and efficacy of the TAMBE System in the treatment of TAAA and PAAA
Study design	Prospective, non-randomized, multicenter
Study population	Primary Study Arm: Type IV TAAA and PAAA Secondary Study Arm: Types I, II, and III TAAA
Sample size	Primary Study Arm: 102 Secondary Study Arm: 20-100
Major inclusion criteria	• Aortic aneurysm involving the visceral vessel(s) requiring treatment defined as at least one of the following: - Fusiform aneurysm diameter ≥5 cm - Saccular aneurysm (no diameter requirement) - Rapid aneurysm growth (≥5 mm in 1 year) • Aortic aneurysm that involves the abdominal aorta, with: - Involvement of at least 1 visceral vessel and aneurysmal extension as far as 65 mm proximal to the celiac artery, and/or - No normal neck between the proximal end of aneurysm and renal artery(s). • Subject assessment favors an endovascular approach when compared to open surgical repair, as deemed by the study investigator. • Appropriate aortic anatomy to receive the TAMBE System.
Primary endpoints	1. Uncomplicated technical success and procedural safety • Technical success of device (successful access and deliver, successful and accurate deployment, and successful withdrawal) at the time of the index procedure • Procedural safety events within the first 30 days of the index procedure (stented segment aortic rupture, lesion-related mortality, permanent paraplegia, permanent paraparesis, new-onset renal failure requiring dialysis, severe bowel ischemia, and disabling stroke) 2. Clinically significant reintervention and lesion-related mortality through 12 months postoperative • Clinically significant reintervention (clinically indicated condition, device effectiveness, subject safety, and complicated device system prophylaxis) • Lesion-related mortality
Secondary endpoints	Standard procedural/hospitalization outcomes • Aneurysm-related mortality • Individual elements of “Procedural safety” • Procedural blood loss • Access-related complications • Procedural time • Length of hospital stay • Extended technical clinical success Aortic stent graft effectiveness measures • Individual elements of “Clinically significant reintervention and lesion-related mortality” • Type I, II, III, and IV endoleak • Device migration • Aneurysm enlargement • Severe distal thromboembolic events • Aortic rupture • Device- or procedure-related laparotomy • Conversion to surgical repair • Aortoiliac device limb occlusion • Loss of device integrity • All reinterventions Branch vessel device effectiveness measures • Branch vessel patency • Acute kidney injury • Renal function deterioration

6.A.(2) Patient characteristics

Table 7 presents the patient characteristics in the clinical study. Table 8 presents the types and diameters of aneurysms.

Table 7. Patient characteristics

		Primary Study Arm	Secondary Study Arm
Sex	Male	82.4% (84/102)	60.0% (15/25)
	Female	17.6% (18/102)	40.0% (10/25)
Race[1]	Caucasian	86.9% (86/99)	84.0% (21/25)
	Black or African American	4.0% (4/99)	8.0% (2/25)
	Asian	2.0% (2/99)	0.0% (0/25)
	Native American or Native Alaskan	2.0% (2/99)	0.0% (0/25)
	Native Hawaiian or Pacific Islander	1.0% (1/99)	4.0% (1/25)
	Others	5.1% (5/99)	4.0% (1/25)
Age (years)[2]		73.3 ± 6.39	73.3 ± 6.55
Body weight (kg)[2]		88.1 ± 18.37	80.8 ± 20.28
Height (cm)[2]		176.2 ± 9.18	172.7 ± 10.05
BMI (kg/m^2)[2]		28.3 ± 5.01	26.8 ± 5.17
Major medical history	Hypertension	92.2% (94/102)	76.0% (19/25)
	Hypercholesterolaemia	84.3% (86/102)	80.0% (20/25)
	Ischemic heart disease	49.0% (50/102)	40.0% (10/25)
	Myocardial infarction	25.5% (26/102)	12.0% (3/25)
	Atrial fibrillation	17.6% (18/102)	4.0% (1/25)
	Arrhythmia	15.7% (16/102)	0.0% (0/25)
	Cardiac failure	7.8% (8/102)	16.0% (4/25)
	Chronic obstructive pulmonary disease	26.5% (27/102)	40.0% (10/25)
	Diabetes mellitus	23.5% (24/102)	8.0% (2/25)
	Renal insufficiency	10.8% (11/102)	8.0% (2/25)

[1] No data on race was collected from subjects in the UK (n = 3).
[2] Mean ± standard deviation (SD)

Table 8. Aneurysm type and diameter

	Primary Study Arm	Secondary Study Arm
Aneurysm diameter[1] (Type I TAAA[2])	-	4.0% (1/25)
<5.0 cm	-	0.0% (0/1)
5.00-5.49 cm	-	0.0% (0/1)
5.50-5.99 cm	-	100.0% (1/1)
≥6.0 cm	-	0.0% (0/1)
Aneurysm diameter[1] (Type II TAAA[2])	-	28.0% (7/25)
<5.0 cm	-	0.0% (0/7)
5.00-5.49 cm	-	28.6% (2/7)
5.50-5.99 cm	-	14.3% (1/7)
≥6.0 cm	-	57.1% (4/7)
Aneurysm diameter[1] (Type III TAAA[2])	-	68.0% (17/25)
<5.0 cm	-	0.0% (0/17)
5.00-5.49 cm	-	23.5% (4/17)
5.50-5.99 cm	-	41.2% (7/17)
≥6.0 cm	-	35.3% (6/17)
Aneurysm diameter[1] (Type IV TAAA[2])	57.8% (59/102)	-
<5.0 cm	0.0% (0/59)	-
5.00-5.49 cm	16.9% (10/59)	-
5.50-5.99 cm	45.8% (27/59)	-
≥6.0 cm	37.3% (22/59)	-
Aneurysm diameter[1] (PAAA[2])	42.2% (43/102)	-
<5.0 cm	2.3% (1/43)	-
5.00-5.49 cm	25.6% (11/43)	-
5.50-5.99 cm	37.2% (16/43)	-
≥6.0 cm	34.9% (15/43)	-

[1] The pre-index procedure aneurysm sizes were baseline values measured at the study sites.
[2] The aneurysm types were determined by Gore Imaging Services (GIS) together with the Screening Committee.

6.A.(3) Medical devices used

Table 9 presents medical devices used during the index procedure in the clinical study.

Table 9. Medical devices implanted during the index procedure

	Primary Study Arm	Secondary Study Arm	
Subjects with the AC implanted	100.0% (102/102)	100.0% (25/25)	
AC proximal diameter × distal diameter × length (mm)	100.0% (102/102)	100.0% (25/25)	
31 × 20 × 160	46.1% (47/102)	0.0% (0/25)	
37 × 20 × 160	53.9% (55/102)	100.0% (25/25)	
Subjects with the BC implanted[1]	100.0% (102/102)	100.0% (25/25)	
Celiac artery, 1 device	57.8% (59/102)	56.0% (14/25)[2]	
2 devices	41.2% (42/102)	40.0% (10/25)	
3 devices	1.0% (1/102)	0.0% (0/25)	
Superior mesenteric artery (SMA), 1 device	49.0% (50/102)	52.0% (13/25)[2]	
2 devices	49.0% (50/102)	40.0% (10/25)[2]	
3 devices	2.0% (2/102)	8.0% (2/25)	
Left renal artery, 1 device	29.4% (30/102)	20.0% (5/25)	
2 devices	58.8% (60/102)	64.0% (16/25)	
3 devices	10.8% (11/102)	12.0% (3/25)	
4 devices	1.0% (1/102)	0.0% (0/25)	
5 devices	0.0% (0/102)	0.0% (0/25)	
6 devices	0.0% (0/102)	4.0% (1/25)	
Right renal artery, 1 device	37.3% (38/102)	24.0% (6/25)	
2 devices	62.7% (64/102)	68.0% (17/25)	
3 devices	0.0% (0/102)	8.0% (2/25)	
Other, 1 device	1.0% (1/102)[3]	4.0% (1/25)[4]	
Subjects with the DBC implanted	100.0% (102/102)	100.0% (25/25)	
Subjects with the CLC implanted	100.0% (102/102)	100.0% (25/25)	
2 devices	52.0% (53/102)	64.0% (16/25)	
3 devices	35.3% (36/102)	20.0% (5/25)	
4 devices	10.8% (11/102)	16.0% (4/25)	
5 devices	1.0% (1/102)	0.0% (0/25)	
6 devices	1.0% (1/102)	0.0% (0/25)	
Subjects with the TC implanted	3.9% (4/102)	100% (18/18)[5]	64.0% (16/25)
1 device	3.9% (4/102)	44.4% (8/18)[5]	48.0% (12/25)
2 devices	0.0% (0/102)	50.0% (9/18)[5]	16.0% (4/25)
3 devices	0.0% (0/102)	5.6% (1/18)[5]	0.0% (0/25)
Subjects with other devices implanted[6]	22.5% (23/102)	12.0% (3/25)	

[1] Total of 23 subjects treated with former products and 2 subjects treated with the second generation delivery system with a smaller diameter (VBX2.0)

[2] One subject whose record wrongly documented the use of 2 devices in the SMA actually had 1 celiac device and 1 SMA device. Fifteen subjects had 1 celiac device, and 14 and 9 subjects had 1 and 2 SMA devices, respectively.

[3] A device was implanted in the left hepatic artery.

[4] The name of the implanted artery was updated to the right renal artery on the electronic data collection system after data lock.

[5] The TC was implanted in 18 of 25 subjects during the preparation procedure for the index procedure.

[6] Other devices included EXC-AEs, bare metal stents, embolization coils, a self-expanding stent graft, and a bovine pericardial patch.

6.A.(4) Study results

6.A.(4).1) Primary Study Arm

6.A.(4).1).(a) Primary Endpoint 1 (Uncomplicated technical success and procedural safety)

Primary Endpoint 1 was analyzed in 102 subjects enrolled in the Primary Study Arm of the clinical study. The percentage of subjects meeting Primary Endpoint 1 was 77.5% (79 of 102 subjects, 95% CI 69.6%-84.1%). The lower limit of the confidence interval did not meet a performance goal of 80%. Table 10 presents the detailed results of Primary Endpoint 1.

Table 10. Summary of uncomplicated technical success and procedural safety (Primary Study Arm)

Endpoint	Percentage % (n/N)
Uncomplicated technical success and freedom from procedural safety events	77.5% (79/102)
Failure to achieve uncomplicated technical success	18.6 (19/102)
Failure of successful access and delivery	0.0 (0/102)
Failure of successful and accurate deployment	18.6 (19/102)
Deployment/kink/twist/placement at unplanned location	1.0 (1/102)[1]
Unplanned placement of non-TAMBE System component	18.6 (19/102)
• Use of non-TAMBE System component to correct iatrogenic complication[2]	3.9 (4/102)
Failure of successful withdrawal	0.0 (0/102)
Procedural safety events[3]	7.8(8/102)
Stented segment aortic rupture	1.0 (1/102)
Lesion-related mortality	0.0 (0/102)
Permanent paraplegia	2.0 (2/102)
Permanent paraparesis	2.9 (3/102)
New-onset renal failure requiring dialysis	2.0 (2/102)
Severe bowel ischemia	0.0 (0/102)
Disabling stroke	1.0 (1/102)

[1] The left renal BC was wrongly placed in the SMA of the subject. Not all essential TAMBE System components could be deployed at planned locations.
[2] Use of a non-TAMBE device component to correct iatrogenic complications in the treated aorta or visceral vessels would be considered as a failure to achieve uncomplicated technical success. Adjudicated by the Clinical Events Committee (CEC).
[3] Adjudicated by the CEC

In the Primary Study Arm, the TAMBE System components included the AC, BC, DBC, and CLC. Use of the TC, which was planned to be used only in the Secondary Study Arm, or the EXC-AE, which was not originally planned to be used in the clinical study, was considered as a "Unplanned placement of non-TAMBE System component." Table 11 presents cases that required placement of additional non-TAMBE System component during the index procedure and were reported as "Unplanned placement of non-TAMBE System component."

Table 11. Subjects with unplanned placement of non-TAMBE System component (Primary Study Arm)

	Treated vessel	Device used	Reason
1	Left renal artery	Bare metal stent	To address BC deformity and smooth transition from the BC to the uncovered blood vessel
2	Right renal artery	Bare metal stent	Right renal artery dissection
3	Abdominal aorta	EXC-AE[2]	Type III endoleak
4	Celiac artery, hepatic artery	Bare metal stent	Wire-related dissection
5	Abdominal aorta	EXC-AE[2]	Type III endoleak
6	Abdominal aorta	EXC-AE[2]	Type III endoleak
7[1]	Left renal artery	Bare metal stent	Left renal artery dissection
8[1]	Thoracic aorta	TC[3]	Type Ia endoleak
9	Abdominal aorta	EXC-AE[2]	Concern of Type Ia endoleak
10	Abdominal aorta	EXC-AE[2]	Type III endoleak
11	Left renal artery	Stent graft[4]	Access failure from the portal to the left renal artery
12	Descending aorta	TC[3]	Type I endoleak
13[1]	Right renal artery	Bare metal stent	Right renal artery dissection
14[1]	Left renal artery	Bare metal stent	Extension after left renal artery dissection
15	Thoracic aorta	TC[3]	Proximal aortic dissection
	Abdominal aorta	EXC-AE[2]	Possible Type Ia endoleak
16	Abdominal aorta	EXC-AE[2]	Type III endoleak
17	Abdominal aorta	EXC-AE[2]	Type III endoleak
18	Thoracic aorta	TC[3]	Descending aortic dissection
19	Abdominal aorta	EXC-AE[2]	Type III endoleak

[1] Considered as "Use of non-TAMBE System component to correct iatrogenic complication"
[2] The DBC Extender Component of the EXCLUDER Bifurcated Endoprosthesis
[3] The Thoracic Component of the Gore CTAG Thoracic Endoprosthesis
[4] Gore Viabahn Endoprosthesis

6.A.(4).1).(b) Primary Endpoint 2 (Clinically significant reintervention and lesion-related mortality)

Primary Endpoint 2 was analyzed in 85 of the 102 subjects enrolled in the Primary Study Arm, excluding 17 subjects (non-lesion-related early death in 6 subjects, failure to return to the site in 7 subjects, and missing scheduled evaluations in 4 subjects). The percentage of subjects who experienced freedom from Primary Endpoint 2 was 70.6% (60 of 85 subjects, 95% CI 61.4%-78.7%). The lower limit of the confidence interval did not meet a performance goal of 68%. Table 12 presents the detailed results of Primary Endpoint 2.

Table 12. Summary of clinically significant reintervention and lesion-related mortality (Primary Study Arm)

Endpoint	Percentage % (n/N)[1]
Freedom from clinically significant reintervention and lesion-related mortality through 12 months postoperative	70.6% (60/85)
Clinically significant reintervention through 12 months postoperative	29.4 (25/85)
Clinically-indicated condition	7.4 (6/81)
Untreated device seal zone endoleak[2]	0.0 (0/82)
Target lesion growth (>5 mm)[2]	6.0 (5/84)
Rupture[3]	1.1 (1/94)
Failure of device effectiveness (compromised device seal zone or integrity)[3]	7.4 (7/94)
Patient safety events (total occlusion of device component)[3]	14.7 (14/95)
Complicated device system prophylaxis (reintervention requiring hospitalization)[3]	4.2 (4/95)
Lesion-related mortality through 12 months postoperative[4]	0.0 (0/94)

[1] The number of subjects analyzed differs among the endpoints because of the differences in the number of subjects shown below among the endpoints.
- Number of subjects who had evaluable data for the endpoint and experienced freedom from the event through 12-month follow-up
- Number of subjects who experienced the event through 12-month follow-up (with or without missing data)

[2] Core Laboratory assessment

[3] Adjudicated by the CEC

[4] All deaths associated with treated lesions or the efficacy of endovascular repair (procedures to address retrograde dissection, loss of patency, loss of device integrity, endoleak, migration, aortic enlargement, or aortic rupture) that occurred during hospitalization for the index endovascular procedure, or within 30 days after the index endovascular procedure or secondary procedure.

Table 13 presents the details of subjects with failure to achieve Primary Endpoint 2.

Table 13. Subjects with failure to achieve Primary Endpoint 2 (Primary Study Arm)

	Aneurysm type	Number of postoperative days (day)	Endpoint	Description
1	Type IV	29	Failure of device effectiveness	Type IIIc endoleak (left renal artery)
2	Type IV	174	Failure of device effectiveness	Stenosis (left renal artery)
3	PAAA	226	Target lesion growth	Aneurysm enlargement due to Type II endoleak[1]
4	PAAA	1	Patient safety event	Occlusion/thrombosis (left renal artery)
5	Type IV	35	Failure of device effectiveness	Type Ic endoleak (left renal artery)
6	PAAA	405	Patient safety event	Occlusion/thrombosis (right renal artery)
7	PAAA	383	Patient safety event	Occlusion/thrombosis (right renal artery)
8	PAAA	0	Complicated device system prophylaxis	Treatment of left renal artery thrombosis
		0	Patient safety event	Occlusion/thrombosis (left renal artery)
9	Type IV	209	Target lesion growth	Aneurysm enlargement due to Type II endoleak[1]
10	Type IV	0	Complicated device system prophylaxis	Treatment of aortic rupture-related retroperitoneal hematoma and hemorrhagic shock
		0	Failure of device effectiveness	Type Ia endoleak
		0	Rupture	Aortic bifurcation rupture[2]
11	PAAA	440	Target lesion growth	Aneurysm enlargement due to Type II endoleak[1]
12	PAAA	14	Patient safety event	Occlusion/thrombosis (right renal artery)
13	Type IV	38	Complicated device system prophylaxis	Treatment of SMA occlusion and mesenteric ischemia
		38	Patient safety event	Occlusion/thrombosis (SMA) and mesenteric ischemia
14	Type IV	198	Patient safety event	Occlusion/thrombosis (right renal artery)
15	Type IV	218	Failure of device effectiveness	Stenosis (right renal artery)
16	Type IV	283	Patient safety event	Occlusion/thrombosis (right renal artery)
17	PAAA	89	Patient safety event	Occlusion/thrombosis (left renal artery)
18	PAAA	250	Target lesion growth	Aneurysm enlargement due to endoleak from an unknown source[1]
19	PAAA	363	Failure of device effectiveness	Stenosis (superior mesenteric artery)
20	Type IV	328	Patient safety event	Occlusion/thrombosis (left renal artery)
21	Type IV	164	Patient safety event	Occlusion/thrombosis (right renal artery)
22	PAAA	471	Target lesion growth	Aneurysm enlargement due to Type II and III endoleaks[1]
		471	Patient safety event	Occlusion/thrombosis (celiac artery)
23	PAAA	31	Failure of device effectiveness	Stenosis (celiac artery, SMA)
24	PAAA	150	Patient safety event	Occlusion/thrombosis (bilateral renal arteries)
25	Type IV	30	Complicated device system prophylaxis	Treatment of acute kidney injury and stent embolism of the bilateral renal arteries
		30	Patient safety event	Occlusion/thrombosis (bilateral renal arteries)

[1] The types of endoleaks reported by the study sites. Aneurysm enlargement was assessed by the Core Laboratory.
[2] A Type Ia endoleak and the collapse of the CLC at the aortic bifurcation were found after the completion of the index procedure. To address the endoleaks, the AC proximal seal zone was re-dilated, followed by ballooning of the bifurcation using kissing balloons to dilate the CLC. A concern for aortic bifurcation rupture was suggested after kissing balloon angioplasty.

6.A.(4).1).(c) Secondary endpoints

Table 14 presents the standard procedural/hospitalization outcomes among the secondary endpoints. Table 15 presents the aortic stent graft effectiveness measures. Table 16 presents branch vessel device effectiveness measures.

Table 14. Standard procedural/hospitalization outcomes (Primary Study Arm)

Endpoint	
Analysis population	102
Procedural blood loss (mL)[1]	
Mean (SD)	299.9 (295.5)
Median	250.0
Range	10.0-2000
Procedural time (min)[1]	
Mean (SD)	315.3 (103.3)
Median	302.5
Range	163.0-944.0
Length of hospital stay (day)[1]	
Mean (SD)	4.9 (3.45)
Median	4.0
Range	1.0-19.0

[1] Reported by the study sites

Table 15. Aortic stent graft effectiveness measures (Primary Study Arm)

Endpoint	N[1]	n
Endoleak[2]	92	68
Type Ia endoleak	81	0
Type Ib endoleak	81	0
Type Ic endoleak	81	0
Type II endoleak	91	64
Type III (unknown) endoleak	81	0
Type IIIa endoleak	81	0
Type IIIb endoleak	81	0
Type IV endoleak	81	0
Endoleak from an unknown source	84	14
Migration[2]	87	0
Aneurysm enlargement[2]	93	5
Severe distal thromboembolic events[3]	95	2
Aortic rupture[3]	94	1
Device- or procedure-related laparotomy[4]	95	4
Conversion to surgical repair[4]	94	0
Aortoiliac device limb occlusion[2]	93	0
Loss of device integrity[2]	86	14
Stent wire fracture	83	3
Device compression	90	11
Kink	87	0
Reintervention[4]	94	15

[1] Subjects with at least 1 evaluable image within the 12-month follow-up period (243-546 days) or those experiencing events that should be included in calculation of aortic stent graft effectiveness measures (except for all reinterventions)
[2] Reported by the Core Laboratory
[3] Adjudicated by the CEC
[4] Reported by the study sites

Table 16. Branch vessel device effectiveness measures (Primary Study Arm)

Endpoint	N[1]	n
Branch vessel patency[2]		
Loss of primary patency	84	23
Loss of assisted primary patency	84	14
Loss of secondary patency	89	10
Acute kidney injury[3]	91	4
Renal function deterioration[4]	74	14

[1] Only subjects who underwent imaging assessment or experienced any relevant event within a given scheduled analysis window were included in calculation of the branch vessel device effectiveness measures.
[2] At 12 months postoperative. Based on duplex ultrasound scanning (DUS) and computed tomography (CT) data. Reported by the Core Laboratory.
[3] At 30 days postoperative. Reported by the study sites. Subjects with estimated glomerular filtration rate (eGFR) data or any relevant event at 1-month follow-up visit were included in the analysis of acute kidney injury.
[4] At 12 months postoperative. Reported by the study sites. Subjects with eGFR data or any relevant event at 12-month follow-up visit were included in the analysis of renal function deterioration.

6.A.(4).1).(d) Safety events

a) Serious adverse events (SAEs)

A total of 44 subjects (44 of 101 subjects, 43.6%) experienced 152 serious adverse events (SAEs) through 12 months postoperative, and 35 procedure-related SAEs in 20 subjects (20 of 101 subjects, 19.8%), 15 device-related SAEs in 8 subjects (8 of 101 subjects, 7.9%), and other SAEs not related to any device, procedure, or medication in 27 subjects (27 of 101 subjects, 26.7%) were reported (Table 17).

Table 17. Procedure- or device-related SAEs (Primary Study Arm)

Event	Number of events	
	Procedure-related	Device-related
Infections and infestations	2	0
Blood and lymphatic system disorders	1	0
Nervous system disorders	5	1
Cardiac disorders	1	0
Vascular disorders	5	0
Respiratory, thoracic and mediastinal disorders	3	0
Gastrointestinal disorders	3	4
Musculoskeletal and connective tissue disorders	2	0
Renal and urinary disorders	7	5
General disorders and administration site conditions	4	5
Injury, poisoning and procedural complications	2	0

b) All-cause deaths

At the time of data lock, there were 11 deaths reported (11 of 102 subjects, 10.8%). Table 18 presents a list of the deaths. Death in 1 subject was Clinical Events Committee (CEC) adjudicated as being related to the study device and death in 1 subject was CEC adjudicated as study procedure related. The remaining subject deaths were not related or unknown. No lesion-related death was reported in the Primary Study Arm through 12 months postoperative. Three subject deaths were not CEC adjudicated since their deaths fell in the >546-day (12-month) analysis window.

Table 18. List of all-cause deaths (Primary Study Arm)

	Study day	Cause of death	Causality relationship	Lesion-related
1	39	Mesenteric ischaemia	Device-related	Not applicable
		Mesenteric arterial occlusion	Device-related	Not applicable
2	60	Acute respiratory failure	Procedure-related	Not applicable
3	66	Type A aortic dissection	Not related	Not applicable
4	88	Small cell lung cancer	Not related	Not applicable
5	108	Unknown	Relationship unknown	Not applicable
6	251	COVID-19	Not related	Not applicable
7	382	Acute respiratory failure	Not related	Not applicable
8	474	Small cell lung cancer	Not related	Not applicable
9	603	Acute kidney injury	Not applicable	Not adjudicated
10	1000	Alzheimer's disease	Not applicable	Not adjudicated
		Failure to thrive	Not applicable	Not adjudicated
11	1030	Haemorrhage intracranial	Not applicable	Not adjudicated

6.A.(4).2) Secondary Study Arm

6.A.(4).2).(a) Primary Endpoint 1 (Uncomplicated technical success and procedural safety)

Primary Endpoint 1 was analyzed in 25 subjects in the Secondary Study Arm. Of them, 23 subjects (23 of 25 subjects, 92.0%) achieved uncomplicated technical success. One subject (1 of 25 subjects, 4%) experienced a procedural safety event of permanent paraparesis. The percentage of subjects who achieved Primary Endpoint 1 was 92.0% (23 of 25 subjects) (Table 19).

Table 19. Summary of uncomplicated technical success and procedural safety (Secondary Study Arm)

Endpoint	Percentage % (n/N)
Uncomplicated technical success and freedom from procedural safety events	92.0% (23/25)
Failure to achieve uncomplicated technical success	8.0 (2/25)
Failure of successful access and delivery	0.0 (0/25)
Failure of successful and accurate deployment	8.0 (2/25)
Deployment/kink/twist/placement at unplanned location	0.0 (0/25)
Unplanned placement of non-TAMBE System component	8.0 (2/25)
• Use of non-TAMBE System component to correct iatrogenic complication[1]	8.0 (2/25)
Failure of successful withdrawal	0.0 (0/25)
Procedural safety events[2]	4.0 (1/25)
Stented segment aortic rupture	0.0 (0/25)
Lesion-related mortality	0.0 (0/25)
Permanent paraplegia	0.0 (0/25)
Permanent paraparesis	4.0 (1/25)
New onset renal failure requiring dialysis	0.0 (0/25)
Severe bowel ischemia	0.0 (0/25)
Disabling stroke	0.0 (0/25)

[1] Use of non-TAMBE device components to correct iatrogenic complications in the treated aorta or branch vessels would be considered as a failure to achieve uncomplicated technical success. Adjudicated by the CEC.
[2] Adjudicated by the CEC

Table 20 presents 2 subjects who required unplanned placement of a non-TAMBE System component and failed successful and accurate deployment.

Table 20. Subjects with unplanned placement of non-TAMBE System component (Secondary Study Arm)

	Treated vessel	Device used	Reason
1	SMA	Bare metal stent	SMA dissection
2	Left renal artery	Coil embolism	Left renal artery perforation
	Aorta	EXC-AE	Possible endoleak

6.A.(4).2).(b) Primary Endpoint 2 (Clinically significant reintervention and lesion-related mortality)

The “clinically significant reintervention through 12 months postoperative” was analyzed in 17 of the 25 subjects enrolled in the Secondary Study Arm, excluding subjects with non-lesion-related early death (4 subjects), failure to return to the site (1 subject), missing scheduled evaluations (1 subject), and failure to complete 12-month follow-up (2 subjects). The “lesion-related mortality through 12 months postoperative” was analyzed in 20 subjects, excluding subjects with non-lesion-related early death (3 subjects) and failure to complete 12-month follow-up (2 subjects). Table 21 presents the detailed results of Primary Endpoint 2. The percentage of subjects who experienced freedom from clinically significant reintervention and lesion-related mortality through 12 months postoperative was 58.8% (10 of 17 subjects). No lesion-related death was reported through 12 months postoperative.

Table 21. Summary of clinically significant reintervention and lesion-related mortality (Secondary Study Arm)

Endpoint	Percentage % (n/N)[1]
Freedom from clinically significant reintervention and lesion-related mortality through 12 months postoperative	58.8% (10/17)
Clinically significant reintervention through 12 months postoperative	41.2 (7/17)
Clinically indicated condition	17.6 (3/17)
Untreated device seal zone endoleak	17.6 (3/17)
Target lesion growth (>5 mm)	0.0 (0/17)
Rupture	0.0 (0/20)
Failure of device effectiveness (compromised device seal zone or integrity)	20.0 (4/20)
Patient safety events (total occlusion of device component)	10.0 (2/20)
Complicated device system prophylaxis (reintervention requiring hospitalization)	5.0 (1/20)
Lesion-related mortality through 12 months postoperative	0.0 (0/20)

[1] The number of subjects analyzed differs among the endpoints because of the differences in the number of subjects shown below among the endpoints.
- Number of subjects who had evaluable data for the endpoint and experienced freedom from the event through 12-month follow-up
- Number of subjects who experienced the event through 12-month follow-up (with or without missing data)

Table 22 presents the details of clinically significant reinterventions.

Table 22. Clinically significant reinterventions (Secondary Study Arm)

	Aneurysm type	Number of postoperative days (day)	Endpoint	Description
1	Type II	0	Failure of device effectiveness	Type IIIa endoleak (SMA)
		6	Untreated device seal zone endoleak	
2	Type III	66	Patient safety event	Occlusion/thrombosis (right renal artery)
3	Type III	41	Untreated device seal zone endoleak	Type Ic endoleak (SMA)
		43	Failure of device effectiveness	
4	Type III	31	Failure of device effectiveness	Type Ic endoleak (SMA), Type IIIa endoleak (right renal artery)
5	Type II	195	Patient safety event	Occlusion/thrombosis (right renal artery)
6	Type III	181	Untreated device seal zone endoleak	Type IIIa endoleak (SMA)
		181	Failure of device effectiveness	
7	Type III	5	Complicated device system prophylaxis	Treatment of Type B aortic dissection

6.A.(4).2).(c) Secondary endpoints

Table 23 presents the standard procedural/hospitalization outcomes among the secondary endpoints. Table 24 presents the aortic stent graft effectiveness measures. Table 25 presents branch vessel device effectiveness measures.

Table 23. Standard procedural/hospitalization outcomes (Secondary Study Arm)

Endpoint	
Analysis population	25
Procedural blood loss (mL)[1]	
Mean (SD)	477.0 (418.0)
Median	300.0
Range	60.0-1750
Procedural time (min)[1]	
Mean (SD)	383.3 (102.4)
Median	371.0
Range	202.0-642.0
Length of hospital stay (day)[1]	
Mean (SD)	7.3 (4.79)
Median	5.0
Range	4.0-23.0

[1] Reported by the study sites

Table 24. Aortic stent graft effectiveness measures (Secondary Study Arm)

Endpoint	N[1]	n
Endoleak[2]	21	14
Type Ia endoleak	17	0
Type Ib endoleak	17	0
Type Ic endoleak	17	1
Type II endoleak	21	12
Type III (unknown) endoleak	17	0
Type IIIa endoleak	17	2
Type IIIb endoleak	17	0
Type IV endoleak	17	0
Endoleak from an unknown source	18	3
Migration[2]	17	1
Aneurysm enlargement[2]	18	0
Severe distal thromboembolic events[3]	20	0
Aortic rupture[3]	20	0
Device- or procedure-related laparotomy[4]	20	1
Conversion to surgical repair[4]	20	0
Aortoiliac device limb occlusion[2]	19	1
Loss of device integrity[2]	18	7
Stent wire fracture	18	7
Device compression	17	1
Kink	17	0
Reintervention[4]	20	6

[1] Subjects with at least 1 evaluable image within the 12-month follow-up period (243-546 days) or those experiencing events that should be included in calculation of aortic stent graft effectiveness measures (except for all reinterventions)
[2] Reported by the Core Laboratory
[3] Adjudicated by the CEC
[4] Reported by the study sites

Table 25. Branch vessel device effectiveness measures (Secondary Study Arm)

Endpoint	N[1]	n
Branch vessel patency[2]		
Loss of primary patency	17	3
Loss of assisted primary patency	17	2
Loss of secondary patency	17	2
Acute kidney injury[3]	19	0
Renal function deterioration[4]	17	3

[1] Only subjects who underwent imaging assessment or experienced any relevant event within a given scheduled analysis window were included in calculation of the branch vessel device effectiveness measures.
[2] At 12 months postoperative. Based on DUS and CT data Reported by the Core Laboratory.
[3] At 30 days postoperative. Reported by the study sites. Subjects with eGFR data or any relevant event at 1-month follow-up visit were included in the analysis of acute kidney injury.
[4] At 12 months postoperative. Reported by the study sites. Subjects with eGFR data or any relevant event at 12-month follow-up visit were included in the analysis of renal function deterioration.

6.A.(4).2).(d) Safety events

a) Serious adverse events (SAEs)

A total of 16 subjects (16 of 21 subjects, 76.2%) experienced 34 SAEs through 12 months postoperative, and 6 procedure-related SAEs in 6 subjects (6 of 21 subjects, 28.6%), 4 device-related SAEs in 4 subjects (4 of 21 subjects, 19.0%), and other SAEs not related to any device, procedure, or medication in 10 subjects (10 of 21 subjects, 47.6%) were reported (Table 26).

Table 26. Procedure- or device-related SAEs (Secondary Study Arm)

Event	Number of events	
	Procedure-related	Device-related
Infections and infestations	0	0
Blood and lymphatic system disorders	0	0
Nervous system disorders	0	0
Cardiac disorders	0	0
Vascular disorders	1	0
Respiratory, thoracic and mediastinal disorders	1	0
Gastrointestinal disorders	0	0
Musculoskeletal and connective tissue disorders	2	0
Renal and urinary disorders	1	0
General disorders and administration site conditions	0	3
Injury, poisoning and procedural complications	1	0
Product issues	0	1

b) All-cause deaths

At the time of data lock, there were 5 deaths reported (5 of 23 subjects, 21.7%). Table 27 presents a list of the deaths. Deaths in 4 subjects were CEC adjudicated as being not related to the procedure or study device. No lesion-related death was reported in the Secondary Study Arm through 12 months postoperative. Death in 1 subject was not CEC adjudicated since the death fell in the >546-day (12-month) analysis window.

Table 27. List of all-cause deaths (Secondary Study Arm)

	Study day	Cause of death	Causality	Lesion-related
1	57	Dementia exacerbation	Not related	Not applicable
2	122	Pulmonary embolism	Not related	Not applicable
3	206	Cardio-respiratory arrest	Not related	Not adjudicated
4	253	Encephalopathy	Not related	Not adjudicated
5	686	Lung cancer	Not applicable	Not adjudicated

6.A.(4).3) Device malfunctions

The study protocol defined device malfunctions as events resulting in insufficient device distinguishability, quality, durability, reliability, safety, or performance. These included operation failure, misuse, and inappropriate indication.

At the time of data lock, the Primary Study Arm had 5 AC-related malfunctions (3 stent wire fractures and 2 deployment failures), 1 BC-related malfunction (patency concern), and a concomitant device (balloon catheter)-related malfunction. The Secondary Study Arm had 4 AC stent wire fractures and 1 TC stent wire fracture. After data lock for the present application, 11 stent wire fractures were additionally reported.

6.B Outline of the review conducted by PMDA

6.B.(1) Extrapolation of foreign clinical data to Japanese patients

The applicant's explanation about the extrapolation of the data from the foreign clinical study to Japanese patients:

The TAMBE System is intended for use only in patients who meet the defined anatomical requirements. The vascular diameter and the anatomical conditions for access routes do not substantially differ between Caucasians and Asians. There appears to be no ethnic factor significant enough to affect the clinical outcome of the TAMBE Device implantation. The Japanese and US guidelines recommend similar treatment policies for aneurysms, for which the TAMBE System is indicated. The clinical outcome of currently available surgical repair does not also substantially differ between Japan and the US. There appears to be no difference between the 2 regions in the medical environment significant enough to affect the clinical outcome of the TAMBE Device implantation. The TAMBE Device implantation involves more complicated procedures than standard endovascular aortic repair (EVAR) and thoracic endovascular aortic repair (TEVAR) in that multiple stent grafts are placed at a target site. It is important to provide users with specified training and information on precautions based on events reported in the clinical study in advance. At the time of the present application, no branched stent graft is approved in Japan or the US. There is no substantial difference in the procedure between these regions that should be considered in assessment of foreign data extrapolation.

PMDA concluded that the applicant's explanation was reasonable and that the results of the clinical study conducted in the US and the UK could be extrapolated to Japan.

6.B.(2) Efficacy and safety

6.B.(2).1) Efficacy and safety in the Primary Study Arm

6.B.(2).1).(a) Primary endpoints

PMDA considers it reasonable to use "uncomplicated technical success and procedural safety (30 days postoperative)" (Primary Endpoint 1) and "clinically significant reintervention and lesion-related mortality (12 months postoperative)" (Primary Endpoint 2) as the primary endpoints in order to evaluate the efficacy and safety of the TAMBE System, and determine their performance goals based on the literature data, etc. on surgical repair and stent grafts. PMDA asked the applicant to explain the reasons that the clinical study failed to meet the performance goals of Primary Endpoints 1 and 2, and

that the applicant nevertheless considered that the results of the clinical study verified the efficacy and safety of the TAMBE System.

The applicant's explanation:
Primary Endpoint 1 (uncomplicated technical success and procedural safety)
The technical failure rate (3%) that was considered in the determination of the performance goal of this endpoint was calculated based on data from previous clinical studies conducted by W. L. Gore & Associates, Inc. These studies were designed to evaluate the efficacy and safety of the stent grafts for the treatment of pathological conditions not requiring treatment of visceral vessels. At the time of creating the protocol of this clinical study, risks of iatrogenic visceral vascular events or additional device implantation were not fully discussed. After the start of the clinical study, the reporting standards for endovascular aortic repair of aneurysms involving the visceral vessels[8] were issued by the SVS, according to which the use of additional devices or procedures during the index procedure should be counted as primary technical success. An additional analysis was performed in 101 subjects in the Primary Study Arm, excluding 1 subject without details of angiography at the completion of the index procedure, using the definition of technical success recommended by the SVS reporting standards. The analysis showed Primary Endpoint 1 of 91.1% (92 of 101 subjects, 95% CI 85.0%-95.3%). The lower limit of the confidence interval exceeded the performance goal. In the analysis, 1 subject (1.0%) did not achieve technical success because of a failure of successful and accurate deployment and 8 subjects (7.8%) experienced procedural safety events within 30 days postoperative.

Table 28 presents the incidence of procedural safety events in the clinical study in comparison with that for surgical repair. The patient characteristics of the clinical study indicate that the clinical study enrolled many subjects who had surgical risk factors listed in the Japanese guidelines (Table 7). The incidence of safety events in the clinical study was lower than that for surgical repair, suggesting that the TAMBE Device implantation can be an effective and safe treatment option available for patients with TAAA or PAAA.

Table 28. Comparison of 30-day mortality and procedure-related events between the Primary Study Arm in the clinical study and literature reports on surgical repair

	Clinical study (Primary Study Arm)	Surgical repair, estimate[1] (Type IV TAAA/PAAA)
Death	0.0% (0/102)	2%-5%
Disabling stroke	1.0% (1/102)	1%-7%
Permanent paraplegia	2.0% (2/102)	0%-2%
Permanent paraparesis	2.9% (3/102)	1%-3%
Intestinal ischaemia	0.0% (0/102)	-[2]
Renal failure requiring dialysis	2.0% (2/102)	2%-5%

[1] The 95% random effect confidence interval based on the data from 29 Japanese and foreign literature reports on surgical repair of TAAA or PAAA
[2] No subgroup analysis of intestinal ischaemia data from the literature reports on surgical repair was performed because only a few of them reported the type of treated aneurysms.

Primary Endpoint 2 (clinically significant reintervention and lesion-related mortality)
While the performance goal of this endpoint was determined based only on the reintervention data reported in the literature reports, the analysis of the results of the clinical study included events not

requiring reinterventions. This difference was not fully assessed in the calculation of the performance goal.

Events classified as “clinically significant reinterventions” occurred in 25 subjects. However, only 15 subjects actually received reinterventions (endoleaks in 4 subjects, endoleak and total occlusion of device component in 1 subject, stent graft stenosis in 3 subjects, total occlusion of device component in 3 subjects, stent graft stenosis and total occlusion of device component in 1 subject, rupture in 1 subject, and others[i] in 2 subjects). The percentage of subjects who experienced freedom from reintervention was 84.8% (95% CI, 76.0%-90.5%). Since there was no lesion-related death through 12 months postoperative, the overall incidence of reinterventions and lesion-related deaths was 15.2% (100% - 84.8% [for freedom from reintervention]). This is consistent with the value (15%) calculated from the literature data on open/branch stent grafts that were used in the determination of the performance goal and the feasibility study of the TAMBE System, suggesting that the incidence of reinterventions in the clinical study is within the expected range in endovascular treatment.

Table 29 presents data on the rates of freedom from aneurysm-related death, which is the original goal of aneurysm treatment, for surgical repair reported in published literature. The aneurysm-related mortality of surgical repair reported in published literature was 0% to 3%, with a 30-day or in-hospital mortality of 0.6% to 3%, although these values vary among the reports. No aneurysm-related death was reported throughout the entire follow-up period in this clinical study. The aneurysm-related mortality of the TAMBE Device implantation appeared to be lower than that of surgical repair.

Table 29. Aneurysm-related mortality of surgical repair

Literature		Number of subjects/ Aneurysm type	Aneurysm-related mortality/time point[1]	30 days or in-hospital mortality[1]
Overseas	Latz et al. 2019[9]	233 subjects/Type IV TAAA	3%/12 months	3% (in-hospital)
	Desole et al. 2019[10]	155 subjects/PAAA	0%/48.6 months (median)	0.6% (30 days)
	Tinelli et al. 2018[11]	119 subjects/PAAA	0%/39.02 months (median)	2.0% (30 days) 2.9% (in-hospital)
	Manunga et al. 2018[12]	69 subjects/PAAA	0%/48 months (mean)	2.9% (30 days)
	Tsai et al. 2012[13]	199 subjects/PAAA	0.5%/56 months (mean)	2.5% (30 days)
Japanese	Sugimoto et al. 2019[14]	88 subjects/PAAA	0%/34.1 months (mean)	No data

[1] Since the definition of aneurysm-related deaths in the clinical study includes all-cause deaths during hospitalization for the index procedure or within 30 days after the index procedure, the aneurysm-related mortality, as well as the 30-day mortality and the in-hospital mortality are also presented in the table.

PMDA’s view on the failure to achieve the performance goals of Primary Endpoints 1 and 2 in the Primary Study Arm:

The re-examination report of the approved abdominal aortic stent graft “Cook Zenith AAA Endovascular Graft” (Approval number, 21800BZY10175000)[15] shows that the percentages of patients who underwent perioperative implantation of additional devices and stents were 9.25% and 19.5%, respectively. Implantation of additional stents, etc. during the stent grafting is an established intervention procedure to ensure the proper placement and function of the stent graft. As recommended by the SVS reporting standards, therefore, the use of additional devices or procedures during the index procedure is reasonably deemed as primary technical success in the clinical study for

[i] The other reasons recorded by the study site were “left renal arterial stenosis” and “left renal arterial stent with infrarenal hyperplasia and distal arterial thrombosis.”

TAAA and PAAA. The applicant's explanation that the performance goal of Primary Endpoint 1 was achieved as shown by the re-analysis based on the SVS reporting standards, was acceptable.

The performance goal of Primary Endpoint 2 was achieved when the definition of "clinically significant reintervention" was adjusted to match the definition in the literature reports which served as the basis for determining the performance goal. The applicant's explanation is basically acceptable.

In the clinical study, neither 30-day death nor 12-month aneurysm-related death was reported (Tables 10, 12, and 18). The TAMBE Device implantation achieved the therapeutic goal for the treatment of aortic aneurysms more safely than surgical repair. The results of the clinical study indicated a certain degree of the efficacy and safety of the TAMBE Device.

The clinical study, however, showed relatively high percentages of subjects requiring unplanned placement of a non-TAMBE System component and subjects experiencing the total occlusion of device components. As aforementioned, additional device implantation is a general practice in stent grafting. Since the structure of the TAMBE System and its procedure are more complicated than those of the approved stent grafts, risk reduction measures, etc. for the TAMBE System, including the total occlusion of the device components, were discussed.

a) Unplanned placement of non-TAMBE System component

The applicant's explanation:

- Additional EXC-AE placement

The EXC-AE was additionally implanted in 9 subjects, and 7 of them received the device to treat or prevent a Type III endoleak in the junction between the AC and DBC. The remaining 2 subjects received the device because of a risk of Type I endoleak at the proximal end of the AC. Neither Type I nor III endoleak was reported in any of these subjects at the completion of the index procedure. None of them experienced any safety event directly related to the additional EXC-AE placement. Since the EXC-AE was not planned to be used as a component of the TAMBE System at the time of designing the clinical study, additional compatibility tests (radiopacity and deployment in a pulsating model) were conducted with the EXC-AE, which is to be used as an option for additional sealing of the junction between the AC and DBC.

- Additional TC placement

The TC was implanted in 4 subjects, and 2 of them received the device because of a Type Ia endoleak. The remaining 2 subjects received the device because of Type B aortic dissection. The additional TC placement in the 2 subjects with a Type Ia endoleak resolved the Type Ia endoleak as confirmed by angiography at the completion of the index procedure. The additional TC placement in the 2 subjects with a Type B aortic dissection improved or stabilized the dissection, with neither aneurysm enlargement nor rupture reported. The Type B aortic dissection in 1 of the subjects was possibly related to balloon inflation or manipulation. Spinal cord ischemia was reported in 2 days postoperative. The event was CEC adjudicated as permanent paraparesis. The remaining 1 subject had no safety event through 30 days postoperative, although the possibility of entry crack caused by the stent proximal to the treated site was recorded. Type B aortic dissection is a known complication of aortic

endovascular treatment. Since its incidence in the clinical study was comparable to that with TEVAR devices, the above cases are clinically acceptable.

- Additional bare metal stent placement

Bare metal stents were implanted in 6 subjects, and 5 of them received the device to address visceral vessel dissections. The causes of the dissections remain unclear. The BC placement, manipulation of the wire or sheath, etc. are suggested to have contributed to the onset of the dissections. All of the dissected visceral vessels were patent at the completion of the index procedure. One subject had the occlusion of the dissected visceral vessel, which recovered its patency after reintervention. No other subject experienced any dissection-related adverse event. The remaining 1 of the 6 subjects with a bare metal stent implanted had a kink distal to the left renal artery, for which a bare metal stent was used in order to smooth out the junction between the stent and the distal renal artery. This subject experienced neither postoperative endoleak nor safety event.

In summary, endoleaks and dissections that require additional non-TAMBE System components are known risks of endovascular treatment and are not risks specific to the TAMBE System. Additional placement of non-TAMBE System components was intended to treat or prevent perioperative complications. It, in itself, does not necessarily risk patients. Any potential risks of placement of these additional devices are reflected in other endpoints of the clinical study for assessment. The analyses of the details of each event that required additional unplanned device placement and the procedural safety events indicate the clinically acceptable safety profile of the TAMBE System although the unplanned placement of non-TAMBE System components contributed to the failure to achieve the performance goal of Primary Endpoint 1 of the clinical study.

The risks of additional placement of non-TAMBE System components can be reduced by providing relevant information on the following issues, similar to that for the conventional stent grafts, in the instructions for use: Balloon inflation and imaging tests of seal zones, the appropriate positioning and placement of the device components, precautions when some resistance is felt in inserting the sheath, catheter, or wire, procedures when additional device placement is required, etc.

PMDA’s view:

The applicant’s policy of reducing the risks of additional placement of non-TAMBE System components by providing relevant information regarding the directions for use, including how to address endoleaks and vascular dissections, was acceptable because these events that resulted in additional placement of non-TAMBE System components are known risks of endovascular treatment and they were technically successfully addressed by using existing endovascular devices in the clinical study, without any clinical event directly related to the additional device placement. However, the TAMBE System, which consists of many components, can be associated with high risks of these events. The TAMBE System should be used by physicians with adequate knowledge and experience in the endovascular treatment of TAAA and PAAA after receiving training.

b) Total occlusion of device component

The applicant's explanation:

There were 22 BC occlusions (2 celiac arteries, 2 SMAs, 6 left renal arteries, and 12 right renal arteries) in 19 subjects (19 of 102 subjects, 18.6%) throughout the entire follow-up period, and 8 events (8 of 22 events, 36.4%) required percutaneous reinterventions. In 5 of them (5 of 8 events, 62.5%), patency was successfully restored (Table 30).

Potential factors that might have been related to the BC occlusions were investigated. The incidence of BC occlusions tended to be high at study sites having limited experience in using the TAMBE System, and in subjects with PAAA and subjects with a small renal artery (≤4-5 mm). The risk of occlusion in small renal arteries is not specific to the TAMBE System. Nevertheless, a warning for the risk of BC occlusion should be provided in the instructions for use. The incidence of BC occlusions through 12 months postoperative was higher in subjects with PAAA (22.0%) than in subjects with Type IV TAAA (9.3%). On the basis of this finding, the TAMBE Device implantation should be limited to high-surgical risk patients with PAAA. Although no clear evidence showing a relationship between experience in the TAMBE Device implantation and BC occlusion is available, BC occlusion tended to occur more frequently at study sites with a limited experience in the TAMBE Device implantation. The incidence of visceral vascular occlusions can be reduced by creating proper criteria for treating physicians and training so as to ensure the proper use of the TAMBE System as with conventional stent grafts.

Table 30. Summary of reinterventions of BC occlusions, patency restoration, function of peripheral organs, and deaths

	Aneurysm type[1]	Occluded vessel	Occlusion Number of postoperative days (day)	Reintervention/treatment	Patency[2] (cause of death for the outcome of death)	Collateral/ peripheral blood flow[3]	Confirmation of renal function deterioration[4]	Start of dialysis Number of postoperative days (day)	Intestinal ischaemia
1	Type IV	SMA	38	None	Death (Mesenteric arterial occlusion)	N/A	N/A	N/A	Present
2	Type IV	SMA	874	None	None	Present	N/A	N/A	None
3	PAAA	Celiac artery	471	None	None	Present	N/A	N/A	N/A
4	Type IV	Celiac artery	787	None	None	Present	N/A	N/A	N/A
5	PAAA	Left renal artery	0	Stent grafting, thrombolysis	Present	Present	1 month	None	N/A
6	PAAA	Left renal artery	1	None	None	Present	1 month	599	N/A
		Right renal artery	592	Stent placement, thrombectomy, tPA	None	N/A	1 month	599	N/A
7	Type IV	Left renal artery	30	Thrombolysis, embolectomy, hemodialysis	Present	Present	1 month	33	N/A
		Right renal artery	30	Thrombolysis, embolectomy	Present	Present	1 month	33	N/A
8	PAAA	Left renal artery	89	Stent placement, thrombectomy, thrombolysis	Present	Present	3 months	None	N/A
9	PAAA	Bilateral renal arteries	150	None	None	Present	6 months	151	N/A
10	Type IV	Left renal artery	328	Balloon angioplasty	None	Present	12 months	None	N/A
11	PAAA	Right renal artery	14	None	None	Present	1 month	27	N/A
12	PAAA	Right renal artery	164	None	None	N/A	None	None	N/A
13	Type IV	Right renal artery	198	Balloon angioplasty, stent placement	Present	Present	6 months	None	N/A
14	Type IV	Right renal artery	283	None	None	Present	12 months	None	N/A
15	PAAA	Right renal artery	383	None	None	N/A	24 months	None	N/A
16	PAAA	Right renal artery	405	None	None	Present	1 month	None	N/A
17	Type IV	Right renal artery	593	Stent placement, balloon angioplasty	Death (Acute kidney injury)	Present	12 months	None	N/A
18	Type IV	Right renal artery	706	None	None	Present	12 months	None	N/A
19	Type IV	Right renal artery	866	None	Death (Haemorrhage intracranial)	N/A	6 months	None	N/A

[1] Reported by study sites, except for the “Aneurysm type” data, which were determined by Gore Imaging Services (GIS) together with the Screening Committee.
[2] Determined based on latest images reviewed before data lock or adverse events reported by study sites after data lock
[3] Collateral/peripheral blood flow status was assessed based on comments from the Core Laboratory. “Present” means the presence of blood flow, blood flow in the collateral circulation, or a persistent contrast distal to an occluded BC as found by the Core Laboratory (regardless of its degree). “None” indicates that there is no description regarding a peripheral blood flow or that there is a description only regarding blood flow in an accessory renal artery(ies). “N/A” refers to no assessment of DUS or CT images after BC occlusion.
[4] Renal function deterioration: A ≥25% decrease in eGFR from baseline after the adverse event of BC occlusion. The first confirmed follow-up visit.

PMDA asked the applicant to explain whether the risk of BC occlusion in the TAMBE Device implantation is clinically acceptable in comparison with the incidence of visceral vascular occlusions in surgical repair, the standard treatment in Japan.

The applicant's explanation:

Table 31 presents the data on BC occlusions in the TAMBE Device implantation (including the events in the Secondary Study Arm) and the incidence of visceral vascular occlusions after surgical repair reported in published literature. Although a comparison is difficult because the sample size, follow-up period, and outcome varied among the literature reports, the incidence of visceral vascular occlusions per artery after surgical repair did not clearly differ from that in the clinical study. On the other hand, the incidence of occlusions per subject tended to be higher in the clinical study. BC occlusion is a known potential risk that is more likely to occur in endovascular treatment, including the TAMBE Device implantation, than surgical repair. A comprehensive risk-benefit balance should be considered for each patient based not only on this risk but also on the mortality and benefits such as perioperative safety to provide the best treatment for the patient.

Table 31. Incidence of visceral vascular occlusions in the clinical study and surgical repair

		Clinical study	Surgical repair (literature)					
			Kahlberg 2018[16]	Tinelli 2018[17]	Tsai 2012[18]	Wang 2020[19]	Mohebali 2021[20]	Latz 2019[21]
Disease		TAAA PAAA	TAAA	PAAA	PAAA	PAAA	TAAA	Type IV TAAA
Sample size, number of target vessels		125 subjects	382 subjects 952 vessels	21 subjects[1]	36 subjects[2]	68 subjects[3]	604 subjects[4]	226 subjects
Follow-up period		Mean, 18.7 months[5]	1, 3, 5 years[6]	Median, 38.9 months[5]	Mean, 56 months[5]	3 years[5]	5 years[6]	Mean. 4.3 years[5]
Onset	Per subject	16.8% (21/125)	-	14.3% (3/21)	-	-	-	4% (10/226)
	Per branch vessel	4.8% (24/499)	2%, 5%, 6%	-	-	-	6%	-
	Celiac artery	1.6% (2/125)	1%, 2%, 2%	-	-	-	1%	-
	SMA	1.6% (2/125)	0%, 0%, 0%	-	-	-	0%	-
	Right renal artery	12.0% (15/125)	0%, 4%, 4%	-	-	2.9% (2/68)	3%	-
	Left renal artery	4.8% (6/124)	9%, 13%, 18%	-	-	8.8% (6/68)	4%	-
	Bilateral renal arteries	8.0% (20/249)	-	-	3% (4/148)	-	-	-

[1] A branch vascular procedure was performed in 21 of 119 patients.
[2] A renal artery bypass surgery was performed in 36 of 199 patients (37 arteries). Images of 136 renal arteries and 12 renal artery bypasses were reviewed.
[3] Follow-up imaging assessment was performed in 68 of 199 patients.
[4] Number of vessels subjected to follow-up assessment: 410 celiac arteries, 406 superior mesenteric arteries, 379 right renal arteries, and 370 left renal arteries
[5] Point estimates
[6] Kaplan-Meier estimates

PMDA's view:

The Primary Study Arm had BC occlusions in 19 of 102 subjects (18.6%), involving 2 SMAs in 2 subjects, 2 celiac arteries in 2 subjects, and 18 renal arteries in 15 subjects. The risk of BC occlusion tended to increase over time and be high in the renal arteries (Table 32). The data suggest a high risk

of BC occlusion in PAAA and small renal arteries, which have only a limited space for BC placement. However, risk factors of BC occlusion and their precautions remain unclear because of a limited sample size for analysis. On the other hand, surgical repair for the treatment of PAAA and TAAA is associated with a relatively favorable patency rate of bypass branch vessels (Table 31). The 5-year patency rate was reportedly 99% in the celiac artery, 100% in the SMA, 97% in the left renal artery, and 96% in the right renal artery.[22] The occlusion of SMA and renal arteries may lead to intestinal ischemia or renal function deterioration, resulting in poor prognosis or severe disorder. Since currently, it is challenging to fully prevent complicating BC occlusion, the indications of the TAMBE must be carefully discussed to ensure that it is used only in patients in whom the benefits of the TAMBE Device implantation outweigh its risks.

Table 32. Cumulative numbers of BC occlusion/thrombosis through 24 months postoperative (Primary Study Arm)

	1 month	3 months	6 months	12 months	24 months
Number of subjects	102	102	97	95	56
Branch vessel occlusion/thrombosis	5 (4.9%)	6 (5.9%)	9 (9.3%)	14 (14.7%)	19 (33.9%)
Celiac artery	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	2 (3.6%)
SMA	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.1%)	2 (3.6%)
Left renal artery	3 (2.9%)	4 (3.9%)	5 (5.2%)	6 (6.3%)	6 (10.7%)
Right renal artery	2 (2.0%)	2 (2.0%)	5 (5.2%)	8 (8.4%)	12 (21.4%)

• The figures through 12 months postoperative include the number of events reported as adverse events and the number of cases based on CEC adjudication. The figures after 24 months postoperative only include the number of events reported as adverse events.
• Follow-up period: 1 month (15-59 days), 3 months (60-126 days), 6 months (127-242 days), 12 months (243-546 days), and 24 months (547-911 days)

6.B.(2).1).(b) Safety of the TAMBE Device

Of serious adverse events in the Primary Study Arm, events assessed as related to the TAMBE Device or its procedure was reported in 7.9% (8 of 101) of subjects and 19.8% (20 of 101) of subjects, respectively. As described earlier in Section “6.B.(2).1).(a) Primary endpoints,” events and endoleaks contributing to the failure to achieve the performance goals of Primary Endpoints 1 and 2, and visceral vascular events are risks occurred at a certain incidence of endovascular treatment with the TAMBE Device. Thorough risk mitigation measures should be taken. The other events were all procedure-related events. They were known procedure-related events in surgical repair and endovascular treatment of these diseases. Those procedure-related events reported in the clinical study are clinically acceptable since their incidences do not tend to be higher than the literature data on conventional therapies.

There were 2 deaths that were CEC adjudicated as being related to the TAMBE Device or its procedure; 1 subject died of mesenteric arterial occlusion and intestinal ischemia related to the TAMBE Device (BC occlusion) and another subject experienced acute respiratory failure at 11 days postoperative and died at 60 days postoperative. To prevent a death due to intestinal ischemia, safety measures must be taken based on the discussion in the previous section “6.B.(2).1).(a).b) Total occlusion of device component.” Although the acute respiratory failure was CEC adjudicated as being

related to the procedure, it was clinically acceptable since the mortality from procedure-related acute respiratory failure is much lower than that for surgical repair.

PMDA's view on the efficacy and safety of the TAMBE System in the Primary Study Arm based on the above discussion:
The clinical study failed to achieve the predefined performance goals. However, reanalyses performed after the definitions of the Primary Endpoints were partially modified according to the new SVS's standards showed that the performance goals were met, with neither perioperative death nor aneurysm-related death reported through 1 year postoperative. The clinical study suggested the efficacy and safety of the TAMBE Device as an endovascular device for the treatment of PAAA and Type IV TAAA. However, visceral vascular occlusion occurred with an incidence of 14.7% through 1 year after the TAMBE Device implantation in the clinical study, with a tendency to increase over time. Not a few subjects experienced serious outcomes including death from intestinal ischemia or renal failure, renal function deterioration, and dialysis.

Surgical repair for the treatment of PAAA and Type IV TAAA is associated with favorable outcomes and a low risk of visceral vascular occlusion. In patients in whom surgical repair can be performed relatively safely, the benefits of the TAMBE Device implantation may not outweigh its risks. For high-surgical risk patients, the TAMBE System can be a valuable treatment option that can address aneurysm rupture relatively safely. Accordingly, the TAMBE Device should be indicated for patients who are not eligible for surgical repair. The efficacy and safety of the TAMBE System can be ensured by taking the measures later described in Section "6.B.(4) Post-marketing safety measures." Taking into consideration the comments from the Expert Discussion, PMDA concluded that the TAMBE Device implantation was useful in Japan.

6.B.(2).2) Efficacy and safety in the Secondary Study Arm

PMDA's view:
It is reasonable to collect and evaluate data on the same endpoints as those for the Primary Study Arm with a focus on potential additional risks of additional TC placement in the Secondary Study Arm because the number of subjects with Type I to III TAAA was limited and the devices, other than the TC, to be used in these subjects were common to subjects with Type IV TAAA and PAAA, who were enrolled in the Primary Study Arm.

The percentage of subjects who achieved Primary Endpoint 1 in the Secondary Study Arm was 92.0% (23 of 25 subjects), which was higher than that in the Primary Study Arm, but "permanent paraparesis" occurred in 1 of 25 subjects (4.0%). In addition, the percentage of subjects who experienced freedom from Primary Endpoint 2 was 58.8% (10 of 17 subjects), which tended to be lower than that in the Primary Study Arm. This can be explained by the higher incidences of the following endoleak-related events: "Untreated device seal zone endoleak" in 17.6% (3 of 17 subjects) and "failure of device effectiveness (compromised device seal zone or integrity)" in 20.0% (4 of 20 subjects).

The applicant's explanation about the higher risks of paraplegia and endoleaks in the Secondary Study Arm:

- Surgical repair for the treatment of Type I to III TAAA is associated with an incidence of paraplegia of 2% to 7% and that of paraparesis of 2% to 5%.[ii] In the Secondary Study Arm in the clinical study, the incidences of paraplegia and paraparesis were 0% and 4%, respectively, showing favorable data compared with surgical repair. Therefore, the risks of paraplegia and paraparesis with the TAMBE System are clinically acceptable.
- There were Type I endoleaks in 2 subjects, Type II endoleaks in 12 subjects, and Type III endoleaks in 3 subjects throughout the entire follow-up period of the currently available data. The Type II endoleaks required no reintervention. Type I and III endoleaks resolved after endovascular treatment. None of them had aneurysm enlargement. The Secondary Study Arm had no endoleak (Type III endoleak between the AC and TC or Type Ia endoleak proximal to the TC) related to TC placement, which was not used in the Primary Study Arm. All of the Type I and III endoleaks occurred with the BC. The clinical study identified no risk of TC placement specific to the Secondary Study Arm. The risk of endoleak is clinically acceptable.

PMDA's view on the efficacy and safety in the Secondary Study Arm:
"Endoleaks requiring reintervention," which was an element of the Primary Endpoint, tended to occur more frequently in the Secondary Study Arm than in the Primary Study Arm. These endoleaks, however, did not lead to clinically significant events such as aneurysm enlargement. No events (including endoleak) related to TC placement, which was required only in the Secondary Study Arm, were reported. BC occlusions occurred in the right renal arteries in 2 of 20 subjects. Treatment failed to restore their patency in either subject, resulting in renal function deterioration. The currently available efficacy and safety data of the TAMBE Device shows neither tendency of being clearly inferior in the Secondary Study Arm compared to the Primary Study Arm nor clinically unacceptable between-arm difference.

The 30-day mortality for surgical repair in Japan was reportedly 7.5%[2] and 2.0%[3] in the treatment of TAAA and PAAA, respectively. The risk of surgical repair is high in patients with TAAA. Although the sample size is limited, the TAMBE Device caused no death through 30 days postoperative, or aneurysm rupture or aneurysm-related death through 12 months postoperative, suggesting a high clinical need for the TAMBE Device. Its usefulness can be expected. However, the sample size of the Secondary Study Arm was as small as 25. It is challenging to accurately predict the efficacy and safety of the TAMBE System in the treatment of TAAA, including the risk of BC occlusion, which was considered a concern in the Primary Study Arm, from the results of this clinical study. Taking into consideration the comments from the Expert Discussion, PMDA concluded that currently, the TAMBE Device should be licensed in Japan for use in not only patients with Type IV TAAA or PAAA, who are high-surgical risk patients requiring less invasive treatment, but also patients with Type I to III TAAA because the latter patient population is also considered to be high-surgical risk patients.

[ii] The 95% random effect confidence interval was calculated from the data from 29 literature reports on surgical repair.

6.B.(2).3) Stent wire fracture

PMDA asked the applicant to explain the sites and root cause analysis of 19 stent wire fractures that occurred in 16 subjects in the clinical study.

The applicant's explanation:

Table 33 presents the details of subjects with stent wire fracture. A root cause analysis of stent wire fractures most commonly reported in the AC sleeve fixation part led to a conclusion that the grafts or other stent wires were unintentionally caught by the sleeve during its fixation in the manufacturing process. To improve the manufacturing process, a change was made to [redacted] which is punctured during fixation of the sleeve, and an in-process test was added to ensure the absence of such inclusion of wires by the sleeve. Three subjects in the Secondary Study Arm, who received the TAMBE Device implantation after the improvements in the manufacturing process in [redacted] 20[redacted], are currently being followed up. One of them had a similar stent wire fracture. A root cause analysis is ongoing.

Subjects with stent wire fractures have had no documented clinical sequela, such as device migration, Type I or III endoleaks, aortic rupture, occlusion, stent interference causing a vascular wall injury (dissection or perforation), embolism, and reinterventions. Based on diagnostic images, continuous follow-up data after fractures, and currently available information from the past bench tests, stent wire fractures of the TAMBE System are unlikely to lead to significant injuries. To mitigate its risks, the manufacturing process has been improved and the stent wire fractures, etc. reported in the clinical study will be notified in post-marketing product training sessions.

Table 33. A list of subjects with stent wire fracture

	Study arm	Date confirmed	Defected device/fracture site	Before/after manufacturing process improvement
1	Secondary	27	AC/Next to PS[1] distal fixation part[2]	Before
2	Secondary	29	AC/Next to PS[1] distal fixation part[2]	Before
3	Secondary	219	TC/Distal apex of proximal stent graft[3]	-[4]
4	Secondary	372	AC/Next to PS[1] distal fixation part[2]	Before
5	Primary	176	AC/Next to PS[1] distal fixation part[2]	Before
		687	AC/Next to DS[5] proximal fixation part[6]	Before
6	Secondary	32	AC/Next to PS[1] distal fixation part[2]	Before
7	Primary	174	AC/Celiac artery and SMA portals[7]	-[4]
8	Primary	377	AC/Next to PS[1] distal fixation part[2]	Before
9	Secondary	750	AC/Next to PS[1] distal fixation part[2]	Before
10	Secondary	442	AC/Left renal artery portal[6]	Before
11	Secondary	363	AC/Left renal artery portal[6]	Before
12	Primary	654	BC/Proximal stent graft in the celiac artery[6]	-[4]
13	Secondary	790	AC/Next to PS[1] distal fixation part[6]	Before
14	Primary	576	BC/Proximal stent graft in the celiac artery[6]	-[4]
15	Secondary	52	AC/Next to PS[1] distal fixation part[6]	After
16	Primary	755	AC/Right renal artery portal[6,8]	Before
			AC/Right renal artery portal[6,8]	
			AC/Right renal artery portal[6,8]	

[1] Proximal sleeve, which secures the proximal end of the AC
[2] The grafts or neighboring stent wires were unintentionally caught by the sleeve during its fixation in the manufacturing process.
[3] Aortic dissection crushed the stent graft, resulting in an increased pressure on the stent wire.
[4] Not applicable because the stent wire fractures occurred in non-AC devices.
[5] Distal sleeve, which secures the distal end of the AC
[6] Root causes are being investigated.
[7] A false lumen blood flow or endoleak associated with the progression of a dissection-induced false lumen resulted in an increased pressure on the stent wire.
[8] Fracture occurred at 3 sites, the first, second, and third rows of the stent distal to the radiopaque marker band on the branch side.

PMDA's view:

The applicant explained that the risks of stent wire fracture reported in the clinical study were clinically allowable because the root cause analysis of the stent wire fractures occurring most commonly at the AC sleeve fixation part led to improvements in the manufacturing process and no adverse event related to the stent wire fractures was reported. The applicant's explanation is acceptable. However, the applicant should continue to evaluate the occurrence and clinical effect of stent wire fractures in the long-term follow-up for the clinical study, and focus on these events in the use-results survey in order to assess the appropriateness of the measures taken by the applicant, long-term effects of the events on clinical outcome, the possibility of stent wire fracture due to other causes, etc. In addition, the applicant should provide relevant information in training sessions so that physicians can identify stent wire fractures and their associated clinical events based on follow-up diagnostic images in clinical practice, and take appropriate measures to address the events.

6.B.(3) Intended use of the TAMBE Device

As described in Section "6.B.(2) Efficacy and safety," the clinical study suggested the generally comparable efficacy and safety profiles of the TAMBE Device to those of surgical repair. No 30-day death occurred. While the clinical study showed the advantage of the TAMBE Device as a less invasive therapy, BC occlusions, as well as their serious complications, including death, intestinal ischemia, and dialysis occurred at a certain incidence. Surgical repair, which is the standard therapy for PAAA and TAAA, is associated with a low risk of branch vessel occlusion. There is only limited clinical data regarding the TAMBE Device in the treatment of TAAA. Based on the above, from the viewpoint of the risk-benefit balance, PMDA concluded that the TAMBE Device should be indicated for patients who are not eligible for surgical repair. To clarify the target aortic aneurysms, the intended use of the TAMBE Device should be modified as shown below:

Intended use or indication (the underlined words are changed)

The GORE EXCLUDER Thoracoabdominal Branch Endoprosthesis is indicated for <u>high-surgical risk</u> patients with thoracoabdominal aortic aneurysms or patients with pararenal aortic aneurysms <u>who meet the anatomical requirements</u>, and used with <u>designated</u> stent grafts <u>whose efficacy and safety have been shown</u> when used in combination with the GORE EXCLUDER Thoracoabdominal Branch Endoprosthesis.

6.B.(4) Post-marketing safety measures

The TAMBE Device is the first thoracoabdominal aortic stent graft to be licensed in Japan, which is intended for use in the treatment of TAAA and PAAA. In order to implement the effective and safe use of the TAMBE in Japan, treating physicians is required to (a) have adequate knowledge in the treatment (medical therapy, surgical repair, and endovascular therapy) of TAAA and PAAA so as to identify eligible patients taking into account the risks for the TAMBE Device implantation versus surgical repair, (b) have adequate knowledge, skills, and experience in TEVAR and EVAR, (c) perform surgical repair of TAAA and PAAA, and appropriately assess and reconstruct relevant visceral vessels, (d) have knowledge and skills regarding diagnosis and procedures required for proper placement of the TAMBE Device, and (e) appropriately treat complications and adverse events related to the TAMBE Device implantation, including emergency measures, and the applicant is required to (f) revise the

guidelines for proper use and take additional safety measures on a timely manner based on post-marketing clinical results.

PMDA concluded that (a) and (d) were reasonable because relevant information, including the anatomical requirements and patient selection criteria, the directions for use, and the precautions based on actual cases, would be provided in product training sessions planned by the applicant (Table 34). PMDA also concluded that (a) to (c), (e), and (f) were reasonable, taking into consideration the comments from the Expert Discussion, and given that the TAMBE Device will be used by physicians with a plenty of experience in the treatment of TAAA and PAAA, for which the TAMBE Device is indicated, at medical institutions with established system in accordance with the guidelines for proper use (draft) prepared by the relevant academic society (the Japanese Committee for Stentgraft Management) shown in Table 35. These requirements should be imposed as Approval Condition 1.

Table 34. Outline of training sessions

Item	Description
Classroom lecture	Product summary, patient selection, implantation procedure, case presentation, diagnostic image assessment, case planning, and sharing of the results of the clinical study
Hands-on training	Device operation under fluoroscopic guidance using an aortic flow model, etc.

Table 35. Summary of the guidelines for proper use (draft)

Item	Description
Criteria for medical institutions	Facilities/instruments and system • Procedures must be conducted in hybrid operating room. • Institutions must have a system qualified for thoracoabdominal aortic aneurysm surgery.[1] Surgical experience[2] • Artificial blood vessel replacement for the treatment of thoracic, abdominal, and thoracoabdominal aortic aneurysms must be conducted on a constant basis. Cooperation by surgeons • Full-time surgeons (i.e., cardiovascular surgery specialists and surgery specialists at medical institutions that have cardiovascular surgery specialists) who have performed artificial vascular reconstruction involving major visceral vessels (celiac artery and superior mesenteric artery) as an operator in at least 5 patients must be in the treating team or can give prompt supports.
Criteria for treating physicians	Basic experience • Treating physicians must be qualified supervisors for all aortic stent grafts that are used in combination with the TAMBE Device, and have experience in using branch stent grafts that are used in combination with the TAMBE Device in at least 5 patients, • Treating physicians must have experience in treating thoracoabdominal aortic aneurysms or pararenal aortic aneurysms (surgery or stent grafting) as an operator or assistant in at least 10 subjects. • Treating physicians must have experience in intervention of visceral vessels (e.g., stent placement and coil embolization) as an operator in at least 10 subjects.* • Treating physicians must have experience in surgery of the abdominal aorta or celiac artery area as an operator in at least 5 subjects.* (*when a treating physician has no experience as an operator, another physician who meets this criterion must directly participate in the treatment.) Obligation of training • Treating physicians must attend a training program on the stent grafts to be used. Use experience • Treating physicians must have experience in successful placement of the stent grafts to be used as an operator in 2 subjects under a supervisory physician.
Criteria for supervisory physicians	Use experience • Supervisory physicians must have experience in stent grafting that they are going to supervise as an operator in at least 10 subjects. Medical practitioner certifications • Physicians certified by the Japanese Association of Cardiovascular Intervention and Therapeutics, specialists certified by the Japanese Society of IVR, specialists certified by the Japanese College of Angiology, cardiovascular surgery specialists, or surgery specialists at medical institutions that have cardiovascular surgery specialists (IVR = Interventional Radiology)
Supplementary	Qualification assessment • Supervisory physicians must qualify treatment physicians based on diagnostic imaging data from the first 10 patients and give advice on device selection, etc.

[1] Such a system must ensure that a medical team including anesthesiologists, nurses, and clinical technicians, executes emergency surgery, including aortic surgery using a heart-lung machine, cerebrospinal fluid drainage for the prevention of paraplegia, and intestinal resection.

[2] The criterion for surgical experience is intended to confirm that vascular operation or endovascular treatment is performed on a regular basis at the medical institution.

7. Plan for Post-marketing Surveillance, etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

Table 36 summarizes the use-results survey plan for the TAMBE Device to evaluate the safety and efficacy of the TAMBE System in post-marketing clinical practice.

Table 36. Use-results survey plan

Objective	To evaluate the safety and efficacy of the TAMBE System in post-marketing clinical practice
Survey population	Patients with thoracoabdominal or pararenal aortic aneurysm who are treated with the TAMBE System during the registration period for this survey
Survey period	9 years ([redacted] years for preparation for sale; [redacted] years for registration; 5 years for follow-up; [redacted] years for survey form collection, data lock, and analysis)
Target sample size	100 (including 18 patients with Type I to III TAAA) Rationale The endpoint of the pivotal study was “uncomplicated technical success and procedural safety.” Of its individual elements, permanent paraplegia and permanent paraparesis occurred with incidences of 1.6% (2 of 125 subjects) and 3.2% (4 of 125 subjects), respectively. The incidence of either event was 4.8% (6 of 125 subjects). Paraplegia is a very significant event in terms of the product concept of the TAMBE System, which is a thoracoabdominal and pararenal branch endoprosthesis. The sample size of this survey must be large enough to assess this event. The sample size of 100 was determined so that permanent paraplegia or permanent paraparesis can be detected in ≥1 patient at a probability of ≥99%.
Methodology	All-case surveillance
Survey items	(a) Preoperative • Patient characteristics, lesion characteristics, etc. • Preoperative test results • Procedure and medical devices used • Information on additional procedures during treatment • Information on adverse events and malfunctions (b) Through 60 months postoperative (1, 6, 12, 24, 36, 48, and 60 months postoperative) • Change in aneurysm diameter • Information on adverse events and malfunctions • Information on reintervention • Conversion to surgical repair • Follow-up cancellation/dropout status

7.B Outline of the review conducted by PMDA

The TAMBE Device is the first stent graft for the treatment of TAAA and PAAA to be licensed in Japan. Information on its efficacy and safety should be collected in clinical practice in Japan through a use-results survey, and additional measures for risk mitigation or proper use should be taken as necessary. Since currently available clinical data on Type I to III TAAA is limited, the survey should focus on the efficacy and safety in these patient populations.

Of branch vessel occlusion-related events, classified as significant adverse events in the clinical study, permanent paraplegia and permanent paraparesis occurred with a similar incidence to that of SMA occlusions and can be potential risks for the TAMBE Device implantation because the area to be treated with the TAMBE System is large. For these reasons, the proposed sample size of 100 is reasonable. The minimum number of patients with Type I to III TAAA of 18 was determined based on the percentage of subjects with Type I to III TAAA enrolled in the clinical study and the estimated number of patients with Type I to III TAAA in Japan.

The results of the clinical study suggest that the efficacy and safety of the TAMBE Device should be carefully evaluated in the post-marketing setting. In addition, the clinical data on this therapy in Type I to III TAAA are limited. Thus, all-case surveillance should be conducted.

The proposed follow-up period of 5 years, which is the same as that of approved stent grafts, is reasonable because the long-term outcome of the TAMBE System has not been fully assessed yet.

PMDA concluded that the draft use-results survey plan proposed by the applicant, including the other proposed survey items, was appropriate and that the conduct of this survey should be imposed as Approval Condition 2. The long-term results of the foreign clinical study are important information which serves as the basis for eligibility assessment for the TAMBE Device implantation, planning of safety measures, etc., follow-up results of the clinical study should be reported annually. This should be imposed as Approval Condition 3.

8. Documents Relating to Information on Precautions, etc. Specified in Paragraph 1 of Article 63-2 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, in Relation to Notification Pursuant to the Same Paragraph of the Act

8.A Summary of the data submitted

The applicant submitted Information on Precautions, etc. (draft) as an attachment in accordance with the Notification titled "Application for Marketing Approval of Medical Devices" (PFSB Notification No. 1120-5, dated November 20, 2014).

8.B Outline of the review conducted by PMDA

On the basis of the conclusion of the Expert Discussion, as described in Section "6.B. Outline of the review conducted by PMDA," PMDA concluded that there were no particular problems with the proposed Information on Precautions, etc., provided that the applicant advises necessary caution.

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

PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

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

IV. Overall Evaluation

The TAMBE Device is a stent graft system intended for use in the treatment of TAAA and PAAA. In the review of the TAMBE Device, PMDA's review primarily focused on (1) the efficacy and safety of the TAMBE Device and (2) post-marketing safety measures. PMDA reached the following conclusions, taking account of comments from the Expert Discussion.

(1) Efficacy and safety of the TAMBE Device

The foreign clinical study conducted to evaluate the safety and efficacy of the TAMBE System in the treatment of TAAA and PAAA failed to achieve the performance goals of the primary endpoints "uncomplicated technical success and procedural safety" and "clinically significant reintervention and lesion-related mortality" in the Primary Study Arm consisting of subjects with Type IV TAAA or PAAA. However, reanalyses performed after the partial modification of the definitions of the primary endpoints showed that the performance goals were met, without perioperative death, or aneurysm rupture or aneurysm-related death through 12 months postoperative. The clinical study demonstrated the efficacy and safety of the TAMBE Device as an endovascular device in the treatment of PAAA and Type IV TAAA. BC occlusions, as well as their serious complications, including death, intestinal ischemia, renal function deterioration, and dialysis occurred at a certain frequency.

The Secondary Study Arm consisting of subjects with Type I to III TAAA tended to have a higher incidence of "endoleaks requiring reintervention," which was an element of the Primary Endpoint, than that in the Primary Study Arm. These endoleaks did not lead to clinically significant events such as aneurysm enlargement. No events related to TC placement, which was required only in the Secondary Study Arm, were reported. Although the number of evaluable subjects was limited, no perioperative death, or aneurysm rupture or aneurysm-related death occurred through 12 months postoperative, suggesting the efficacy and safety of the TAMBE Device in the treatment of Type I to III TAAA.

The 30-day mortality for surgical repair in Japan was reportedly approximately 7.5%[2] and 2.0%[3] in the treatment of TAAA and PAAA, respectively. The data suggest the clinical need for the TAMBE Device that was not associated with death in 30 days postoperative. The risks of BC occlusions and their serious complications, including death, intestinal ischemia, renal disorder, and dialysis, are currently unavoidable. Surgical repair, the standard treatment, is associated with a low risk of branch vessel occlusion. There is only limited clinical experience with use of the TAMBE Device in the treatment of TAAA and PAAA. Based on the above, from the viewpoint of the risk-benefit balance, PMDA concluded that the TAMBE Device should be indicated for patients with TAAA or PAAA who are not eligible for surgical repair.

(2) Post-marketing safety measures

The TAMBE Device will be the first branch stent graft system in Japan, which is intended for use in the treatment of TAAA and PAAA. In order to implement the effective and safe use of the TAMBE System in Japan, physicians and medical team members with adequate knowledge and experience in the treatment of the target diseases acquire the necessary knowledge and skills regarding the TAMBE System and relevant procedures through training sessions and other learning opportunities and identify patients eligible for the treatment taking into account the risks of the TAMBE System versus surgical repair. Since perioperative or postoperative complications need immediate medical interventions including surgery, the TAMBE Device implantation should be performed at medical institutions with an established system for emergencies. PMDA concluded that adherence to the guidelines for proper

use prepared by relevant academic societies was also important and that this should be imposed as Approval Condition 1.

PMDA also concluded that the applicant should collect information on the relevant procedures and skills required for the use of the TAMBE System, adverse events including branch vessel occlusions, long-term outcomes, and other necessary information through a use-results survey, and take additional risk reduction measures as necessary. The use-results survey period of the TAMBE Device should be 9 years ([redacted] years for preparation for sale; [redacted] years for registration; 5 years for follow-up; [redacted] years for survey form collection, data lock, and analysis), which should be imposed as Approval Condition 2.

Since the long-term results of the foreign clinical study are important information which serves as the basis for eligibility assessment for the TAMBE Device implantation, planning of safety measures, etc., follow-up results of the clinical study should be reported annually. This should be imposed as Approval Condition 3.

As a result of the above review, PMDA has concluded that the TAMBE Device may be approved for the intended use shown below.

Intended Use

The GORE EXCLUDER Thoracoabdominal Branch Endoprosthesis is indicated for high-surgical risk patients with thoracoabdominal aortic aneurysms or patients with pararenal aortic aneurysms who meet the anatomical requirements, and used with designated stent grafts whose efficacy and safety have been shown when used in combination with the GORE EXCLUDER Thoracoabdominal Branch Endoprosthesis.

Approval Conditions

1. The applicant is required to take necessary measures, such as dissemination of the guidelines for proper use of the product prepared in cooperation with relevant academic societies and delivery of seminars, to ensure that physicians and medical team members with adequate knowledge and experience in the treatment of thoracoabdominal aortic aneurysms and pararenal abdominal aortic aneurysms acquire full skills of the product usage and knowledge in complications associated with the procedure and identify patients eligible for the treatment and that the physicians use the product at medical institutions with an established system for the treatment.
2. The applicant is required to conduct a use-results survey involving all patients treated with the product in the post-marketing setting until data from a specified number of patients have been accrued, thereby reporting the survey results to the Pharmaceuticals and Medical Devices Agency and taking other appropriate measures as necessary.
3. The applicant is required to submit annual reports on the results of analysis of the long-term outcome of the patients treated in the clinical study included in this regulatory submission to the Pharmaceuticals and Medical Devices Agency and to take appropriate measures as necessary.

The product is not classified as a biological product or a specified biological product. The product is designated as a medical device subject to a use-results survey. The use-results survey period should be 9 years.

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

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