January 15, 2016
Medical Device and Regenerative Medicine Product Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Heparin-coated stent-graft for central circulatory system Heparin-coated stent-graft for blood vessels
Brand Name	Gore Viabahn Stent Graft
Applicant	W. L. Gore & Associates, G.K.
Date of Application	June 3, 2015 (Application for marketing approval)

Results of Deliberation

In its meeting held on January 15, 2016, 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 Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Approval Conditions

Treatment of traumatic or iatrogenic vascular injuries

1. The applicant is required to ensure that the product is used by physicians with a full understanding of the efficacy and safety of the product, as well as adequate knowledge and experience in treating traumatic or iatrogenic vascular injuries to the arteries in the chest, abdomen, or pelvis in compliance with the approved indications of the product. For this purpose, the applicant must take necessary measures to ensure that physicians follow the guidelines for proper use of the product prepared in collaboration with relevant academic societies and take necessary educational programs.
2. The applicant is required to take necessary measures in cooperation with related academic societies to ensure that the product is used by physicians who meet the requirements in 1 above at medical institutions capable of taking necessary measures in the event of an emergency including stent graft-related complications.

Vascular patency treatment

The applicant is required to report to the Pharmaceuticals and Medical Devices Agency the results of a periodic analysis of long-term prognosis in patients participating in the submitted clinical study and take appropriate measures.

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Review Report

December 16, 2015

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	Heparin-coated stent-graft for central circulatory system (to be newly created) Heparin-coated stent-graft for blood vessels (to be newly created)
Brand Name	Gore Viabahn Stent Graft
Applicant	W. L. Gore & Associates, G.K.
Date of Application	June 3, 2015
Items Warranting Special Mention	Priority review
Reviewing Office	Office of Medical Devices II

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Review Results

December 16, 2015

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Heparin-coated stent-graft for central circulatory system (to be newly created) Heparin-coated stent-graft for blood vessels (to be newly created)
Brand Name	Gore Viabahn Stent Graft
Applicant	W. L. Gore & Associates, G.K.
Date of Application	June 3, 2015
Items Warranting Special Mention	Priority review

Results of Review

Gore Viabahn Stent Graft is Japan's first stent graft system for peripheral blood vessels. The system consists of a stent graft with an external nitinol stent wire wound around the stent-graft structure and a delivery catheter. The graft of Gore Viabahn Stent Graft is made of polytetrafluoroethylene. Both surfaces of the stent graft have a heparin-bonding layer processed from heparin sodium.

The applicant submitted nonclinical data supporting the physicochemical properties, biological safety, stability and durability, and performance, indicating no particular problem.

To support the clinical evaluation of Gore Viabahn Stent Graft in vascular injury treatment, the applicant submitted a clinical evaluation report based on 22 publications that reported the treatment of 33 cases of traumatic or iatrogenic vascular injuries to the subclavian, iliac, superior mesenteric, or hepatic artery with Gore Viabahn Stent Graft or its previous generation Hemobahn.

The efficacy evaluation in this report showed that a total of 32 patients (97.0%), including patients who required additional treatment, achieved primary hemostasis. There are sufficient data regarding the clinical experience with stent grafts, including similar medical devices, in vascular injury treatment. In addition, the nonclinical results of Gore Viabahn Stent Graft verified its hemostatic effect. Given this and on the basis of the submitted clinical evaluation report that verified the hemostatic effect of Gore Viabahn Stent Graft, PMDA concluded that Gore Viabahn Stent Graft is clinically effective in hemostasis. The application sites (blood vessels) of Gore Viabahn Stent Graft should include not only the subclavian and iliac arteries, in which the effect of Gore Viabahn Stent Graft was reported in multiple publications, but also the abdominal aortic branches.

The safety evaluation of Gore Viabahn Stent Graft revealed many occlusion-related adverse events, i.e., 2 events of graft occlusion, 2 events of stenosis, 2 events of thromboembolism, and 2 events of collateral occlusion. However, Gore Viabahn Stent Graft was not associated with re-hemorrhage or death. PMDA concluded that these adverse events are clinically acceptable because the main trunk is closed to achieve hemostasis in vascular injury treatment. Considering the limited options of hemostatic medical devices available for emergency life-saving purposes and the lack of approved peripheral stent grafts, it is of significance to make Gore Viabahn Stent Graft available in clinical practice. However, the adequate long-term safety data of Gore Viabahn Stent Graft has not been available. Therefore, instructions for use

should clearly state that Gore Viabahn Stent Graft is intended to be used for emergency life-saving purposes and caution that sufficient observations are required after temporary hemostasis is achieved.

To minimize the risk of treatment with Gore Viabahn Stent Graft in the post-marketing setting, 1) physicians who have received education and training and have sufficient knowledge about the anatomical requirements of vascular injury sites should select appropriate treatment methods and devices including conventional treatments, and 2) physicians who have sufficient experience in addressing problems, such as unsuccessful hemostasis and complications, should use Gore Viabahn Stent Graft. Since currently no prospective clinical data are available and a very limited number of cases have been reviewed in the publications, use-results surveys should be conducted to collect the efficacy and safety information of Gore Viabahn Stent Graft. On the basis of such newly available information, appropriate measures must be taken.

To support the clinical evaluation of Gore Viabahn Stent Graft in vascular patency treatment, the applicant submitted the results from a Japanese clinical study in patients with a ≥10 cm symptomatic stenotic or occlusive lesion in the femoropopliteal artery. The efficacy evaluation showed an assisted-primary patency rate of 91.0%, which met the performance goal established with reference to the results of bypass surgeries. The clinical success rate, defined as ≥1 improvement in Rutherford category at 12 months post-procedure, was 90.9% (90 of 99 patients). The safety evaluation showed stent graft occlusion and stenosis likely caused by in-stent thrombosis. Gore Viabahn Stent Graft has a covered stent structure, unlike conventional stents for superficial femoral artery (SFA). Gore Viabahn Stent Graft is used in longer-segment lesions than those that are treated with conventional stents. Given these points, patients treated with Gore Viabahn Stent Graft after the market launch should receive dual antiplatelet therapy (DAPT) with at least 2 agents for a certain period. The recommended duration of DAPT must be communicated to healthcare professionals. Considering the risk of the prolonged use of DAPT with Gore Viabahn Stent Graft compared with that with conventional metal stents used to treat lesions in the SFA, it is essential to make decisions on whether to use Gore Viabahn Stent Graft after fully assessing its risk-benefit balance. This should be included in the instructions for use. In the use-results surveys, information regarding stent fractures, stent thrombosis, etc. especially in long-segment lesions must be collected to take appropriate risk mitigation measures.

As a result of its review, PMDA has concluded that Gore Viabahn Stent Graft may be approved for the intended use shown below, with the following approval conditions, and concluded that the application should be deliberated by the Committee on Medical Devices and *In-vitro* Diagnostics.

Intended Use

Gore Viabahn Stent Graft is indicated for emergency treatment of patients who have blood leakage that is difficult to manage due to a traumatic or iatrogenic injury to the thoracic, abdominal, or pelvic artery with a reference vessel diameter of 4.0 to 12.0 mm, excluding injuries to the aorta, coronary artery, brachiocephalic artery, carotid artery, vertebral artery, and pulmonary artery.

In addition, Gore Viabahn Stent Graft is indicated for improving blood flow in patients with symptomatic peripheral arterial disease having a ≥10 cm lesion in the SFA with a reference vessel diameter ranging from 4.0 to 7.5 mm.

Approval Conditions

Treatment of traumatic or iatrogenic vascular injuries

1. The applicant is required to ensure that the product is used by physicians with a full understanding of the efficacy and safety of the product, as well as adequate knowledge and

experience in treating traumatic or iatrogenic vascular injuries to the arteries in the chest, abdomen, or pelvis in compliance with the approved indications of the product. For this purpose, the applicant must take necessary measures to ensure that physicians follow the guidelines for proper use of the product prepared in collaboration with relevant academic societies and take necessary educational programs.

2. The applicant is required to take necessary measures in cooperation with related academic societies to ensure that the product is used by physicians who meet the requirements in 1 above at medical institutions capable of taking necessary measures in the event of an emergency including stent graft-related complications.

Vascular patency treatment

1. The applicant is required to report to the Pharmaceuticals and Medical Devices Agency the results of a periodic analysis of long-term prognosis in patients participating in the submitted clinical study and take appropriate measures.

Review Report

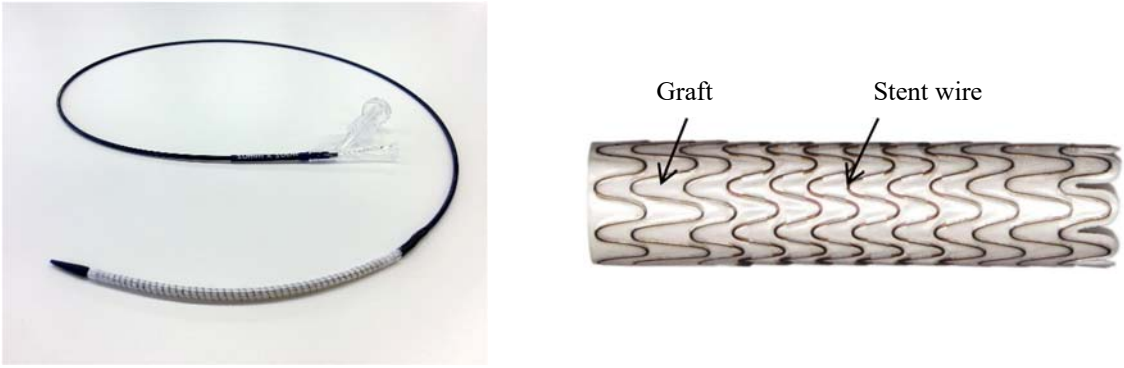
December 16, 2015

I. Product for Review

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Heparin-coated stent-graft for central circulatory system (to be newly created) Heparin-coated stent-graft for blood vessels (to be newly created)
Brand Name	Gore Viabahn Stent Graft
Applicant	W. L. Gore & Associates, G.K.
Date of Application	June 3, 2015
Proposed Intended Use	Gore Viabahn Stent Graft is indicated for improving blood flow in patients with symptomatic peripheral arterial disease having a ≥10 cm lesion in the femoropopliteal artery with a reference vessel diameter ranging from 4.0 to 7.5 mm. Gore Viabahn Stent Graft is indicated for the treatment of a traumatic or iatrogenic injury to the thoracic, abdominal, or pelvic artery with a reference vessel diameter of 4.0 to 12.0 mm, excluding injuries to the aorta, coronary artery, brachiocephalic artery, and carotid artery.
Items Warranting Special Mention	Priority review

II. Product Overview

Gore Viabahn Stent Graft consists of a stent graft with an external nitinol stent wire wound around the supporting stent-graft structure (hereinafter referred to as Stent Graft) and a delivery catheter (hereinafter referred to as Catheter) (Figure 1). The graft of Stent Graft is made of polytetrafluoroethylene (PTFE). Both surfaces of the stent graft have a heparin-bonding layer fused with heparin sodium.



(a) Entire delivery system (b) Stent graft

Figure 1. Exterior appearance of Gore Viabahn Stent Graft

Table 1 shows the available stent graft sizes for each indication. The 9 to 13 mm diameter devices are used only for traumatic or iatrogenic vascular injury treatment (vascular injury treatment), while the 25 cm length device is used only for treatment of stenosis or occlusion lesions (vascular patency treatment).

Two types of Stent Graft, with or without radiopaque markers, are available. Both types are made of the same raw materials and have the same basic structure.

The Catheter in which Stent Graft is placed is available in 3 types: Catheter A (5-8 mm diameter Stent Graft, 0.035 inch guidewire), Catheter B (9-13 mm diameter Stent Graft, 0.035 inch guidewire), and Catheter C (5-8 mm diameter Stent Graft, 0.014 or 0.018 inch guidewire). Catheter B is made of the same raw materials as Catheter A, except for the tip of Catheter B, which is made of more types of materials. Catheter C has the same basic structure as Catheters A and B, while the main raw materials of Catheter C differ from those of Catheters A and B.

Table 1. Stent graft sizes available for each indication

Diameter (mm)	Stent graft lengths available for each indication (cm)	
	Vascular injury treatment	Vascular patency treatment
5, 6, 7, 8	2.5, 5.0, 7.5, 10.0, 15.0	2.5, 5.0, 7.5, 10.0, 15.0, 25.0
9	5.0, 7.5, 10.0, 15.0	—
10	2.5, 5.0, 10.0, 15.0	—
11	2.5, 5.0, 10.0	—
13	2.5, 5.0, 10.0	—

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

The data submitted in this application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below. The expert advisors present during the Expert Discussion on Gore Viabahn Stent Graft 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).

Gore Viabahn Stent Graft has been applied for approval for the 2 intended uses, vascular injury treatment and vascular patency treatment. In the following sections, the information is provided separately for each intended use as necessary.

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

1.A Summary of the data submitted

1.A.(1) History of development

1.A.(1).(a) Vascular injury treatment

Vascular injury treatment includes treatment of traumatic vascular injuries and iatrogenic vascular injuries. Traumatic vascular injuries include injuries caused by traffic accidents. These types of vascular injuries are manifested as hemorrhage, shock, and other various symptoms. They are often accompanied by infection or multiple injuries. Diagnosis and treatment of traumatic vascular injuries should focus on life-saving. In principle, immediate diagnosis and treatment of bleeding sites are given priority.

On the other hand, iatrogenic vascular injuries include malpuncture and vascular injuries caused by catheterization for therapeutic or diagnostic purposes. Iatrogenic vascular injuries to the thoracic, abdominal, or pelvic artery rarely occur. However, these types of vascular injuries require immediate hemostasis because loss of blood can be fatal.

In Japan, vascular injuries are treated through surgery, coil embolization, or angiopressure with a balloon. Endovascular treatment is also often performed when surgical treatment alone cannot provide hemostasis or for other reasons. If treatment using a coil, balloon, etc. appears not to be successful because of the lesion site or severity, the limb part of a covered stent for the bile duct or stent graft for

the aorta is used in an off-label manner for emergency purposes. Currently, "Graft Master" (Approval number 21500BZY00239000), which is used to save lives in the case of perforation in the coronary or saphenous vein graft, and "Gore CTAG Thoracic Endoprosthesis" (Approval number 22500BZX00427000), which is used for traumatic injuries to the thoracic aorta, are only endovascular treatment devices approved for vascular injury treatment in Japan. It is of a great significance to make Gore Viabahn Stent Graft, which can be used in the peripheral arteries, available in Japan. Given this situation, Gore Viabahn Stent Graft was selected at the "15th Meeting of the Study Group on Early Introduction of Highly Needed Medical Devices, etc. (the Needs Study Group)" in 2009 for the intended use of "endovascular treatment of aneurysms, or traumatic or iatrogenic vascular injury to the iliac artery or superficial femoral artery (SFA)."

1.A.(1).(b) Vascular patency treatment

Peripheral arterial disease (PAD) is a circulation disorder caused by peripheral arterial stenosis or occlusion. In recent years, PAD is profoundly increasing in prevalence and severity as the number of atherosclerosis is increasing because of aging population and Westernization of lifestyle.[1] PAD is often accompanied by arteriosclerotic diseases, including ischemic heart disease and brain disease, and the prognosis of PAD is poor, thus, early diagnosis and appropriate treatment are essential. Given this situation, a number of academic societies in the US and European countries have prepared a joint global medical practice guideline for PAD whose prevalence is growing all over the world. Subsequently, Trans-Atlantic Inter-Society Consensus II (TASC II), an internationally standardized medical practice guideline for PAD, was revised in 2007 by 16 academic societies in the above countries and Asian countries, including the Japanese College of Angiology. TASC II has been used as a medical practice guideline for PAD worldwide (Table 2).

Table 2. Treatment guideline for femoropopliteal artery lesions (TASC II classification)

Lesion		Recommended treatment
Type A lesions	• Single stenosis ≤10 cm in length • Single occlusion ≤5 cm in length	Endovascular treatment is the first-line treatment.
Type B lesions	• Multiple lesions (stenosis or occlusion), each ≤5 cm in length • Single stenosis or occlusion ≤15 cm in length, not involving the infrageniculate popliteal artery • Single or multiple lesions in the absence of continuous tibial arteries to improve inflow for a distal bypass • Heavily calcified occlusion ≤5 cm in length • Single popliteal arterial stenosis	Endovascular treatment is recommended.
Type C lesions	• Multiple stenoses or occlusions totaling >15 cm in length with or without heavy calcification • Recurrent stenoses or occlusions that need treatment after 2 endovascular interventions	Surgical therapy is recommended.
Type D lesions	• Chronic total occlusion of the common or SFA (>20 cm, involving the popliteal artery) • Chronic total occlusion of the popliteal artery and proximal trifurcation vessels	Surgical therapy is the first-line treatment.

Stent Graft was developed as an endovascular treatment device that was intended to play the similar role as surgical bypass using an artificial graft(s) in that healthy central and peripheral blood vessels from a lesion are connected with a stent graft made of the same materials as PTFE artificial blood vessels to achieve revascularization. The efficacy of endovascular treatment using general balloons (plain old balloon angioplasty [POBA]), metal stents (bare metal stent [BMS]), etc. is known to decrease in terms of vascular patency in proportion to the lesion length.[2-3 4] TASC II recommends that vascular treatment be limited to short lesions, Types A and B. Gore Viabahn Stent Graft is expected to show a certain level of efficacy without being profoundly influenced by the lesion length and track easily through even highly curved blood vessels because of its highly flexible stent compared with conventional stents. Gore

Viabahn Stent Graft was developed to be applied to Type C or D lesions to which surgery is generally recommended.

1.A.(1).(c) History of development of Gore Viabahn Stent Graft

Gore Viabahn Stent Graft was developed by W. L. Gore & Associates, Inc. In the US, Hemobahn, the previous generation product of Gore Viabahn Stent Graft, received 510(k) clearance in 2002 as a stent graft for the treatment of bronchostenosis due to malignant tumor and subsequently a pre-market approval (PMA) in 2005 as a stent graft for the treatment of stenotic or occlusive PAD in the SFA. Gore Viabahn Stent Graft was given a PMA in 2007 as an improved product of Hemobahn. Gore Viabahn Stent Graft is not approved for vascular injury treatment in the US.

In Europe, on the other hand, a CE mark was given to Hemobahn in 1996 as a peripheral stent graft without limiting its intended use and to Gore Viabahn Stent Graft in 2008 as an improved product of Hemobahn.

This regulatory submission also included studies and publications of Hemobahn. Table 3 shows key differences between Hemobahn and Gore Viabahn Stent Graft. Stent Graft has the same structure and raw materials as Hemobahn, except for the secondary fiber helix, heparin-bonding layer, radiopaque markers, wavy shape of stent end, and size line-up.

Table 3. Key differences between Hemobahn and Gore Viabahn Stent Graft

	Gore Viabahn Stent Graft	Hemobahn
Stent graft		
Secondary fiver helix*[1] (Figure 2)	No	Yes
Heparin-bonding layer	Yes	No
Radiopaque marker	Yes/No	No
Inside diameter	5-13 mm	6-13 mm
Length	2.5-25 cm	2.5-15 cm
Wavy shape of stent graft end (at the proximal end of the delivery catheter)*[2] (Figures 3 and 4)	Yes	No
Delivery system		
Stent graft placement (Figure 5)	• [redacted] •	• [redacted] •
Direction of stent graft deployment (Figure 6)	From the tip to the hub	From the hub to the tip
Delivery system profile*[3]	6-12 Fr	8-12 Fr
[redacted]		

*3: The diameter was decreased to achieve a low profile, etc.

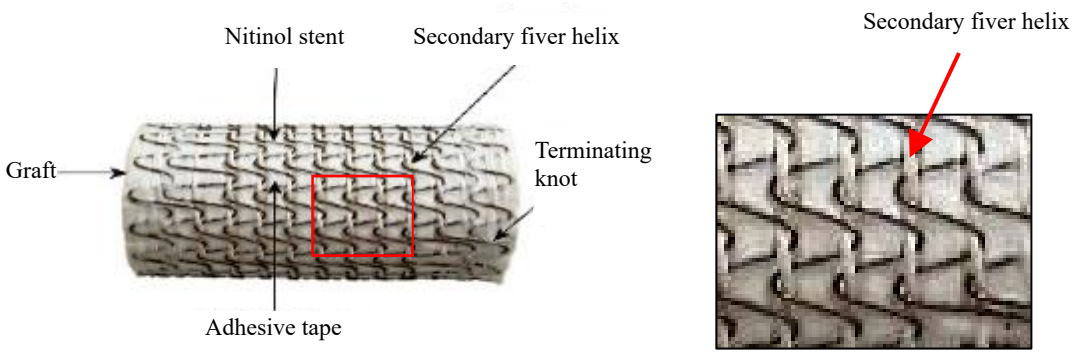
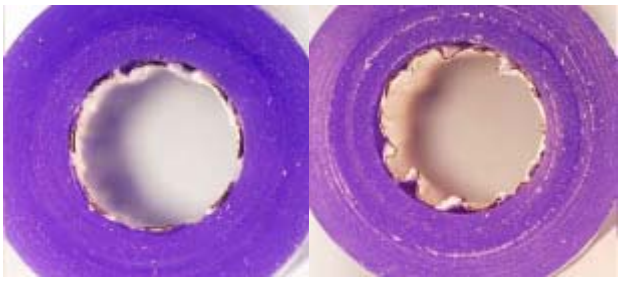


Figure 2. Secondary fiver helix (Hemobahn)

(a) Wavy end
(Gore Viabahn Stent Graft)

(b) No wavy end
(Hemobahn)

Figure 3. Shape of stent graft end (only one end)

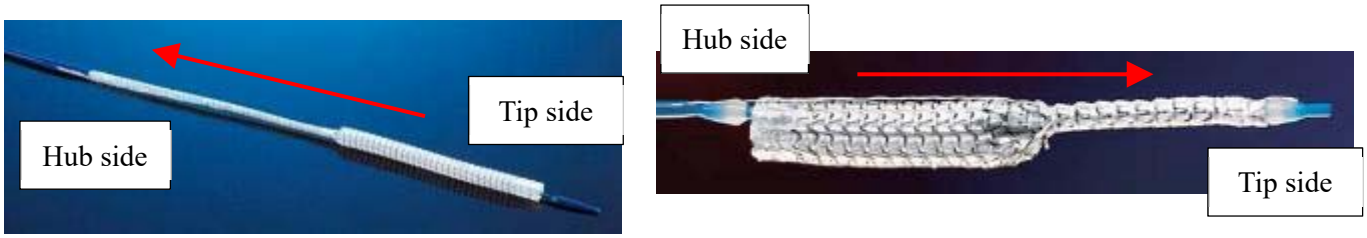


(a) Wavy end (b) No wavy end

Figure 4. Cross-section view of the 6 mm diameter stent graft inserted into the 5 mm tube

(a) Gore Viabahn Stent Graft (b) Hemobahn

Figure 5. Placement of stent graft (cross-section view)



(a) Gore Viabahn Stent Graft (b) Hemobahn

Figure 6. Deployment method of stent graft (entire view)

1.A.(2) Use in foreign countries

Gore Viabahn Stent Graft, including the overseas product without a heparin-bonding layer, is commercially available in the US, Europe, and other countries. As of June 2015, its overseas total sales number is [redacted] ([redacted] including the previous generation product of Gore Viabahn Stent Graft).

1.A.(3) Malfunctions of Gore Viabahn Stent Graft or similar medical devices

Table 4 shows malfunctions of Gore Viabahn Stent Graft reported during the period from the start of its sales in the US, Europe, and other countries to June 30, 2015, including malfunctions of the product without a heparin-bonding layer that is available overseas. The information in this table covers all malfunctions reported to the regulatory authorities regardless of these countries/regions or regardless of whether the devices were used in an on- or off-label manner.

Table 4. Incidences of malfunctions reported in foreign countries

Malfunction	Number of malfunctions N = [redacted]	Incidence
Additional surgical intervention	[redacted]	0.031%
Additional non-surgical intervention		0.024%
Deployment failure		0.019%
Occlusion		0.018%
Endoleak		0.010%
Component breakage		0.008%
Death		0.008%
Stent distortion		0.007%
Migration		0.006%
Device removal		0.006%
Failure of catheter advancement		0.005%
Early deployment		0.005%
Device or device component remaining in the body		0.005%
Thrombosis		0.004%
Bend		0.004%
Heparin-induced thrombocytopenia (HIT)		0.004%
Difficulty of catheter removal		0.004%
Vessel perforation		0.003%
Device fracture		0.003%
Infection		0.003%
Insertion difficulty		0.002%
Kink		0.002%
Inaccurate delivery		0.002%
Difficulty of deployment		0.002%

The reported cases of "additional surgical intervention" included those requiring any surgical intervention, including not only surgical bypass and device removal but also surgical cut-down, e.g., a change from percutaneous access to open surgical access to remove a partially deployed device. The incidence of additional surgical intervention was 0.031% on a device basis ([redacted] patients on a patient basis). Of [redacted] patients on a patient basis, [redacted] patients (72.9%) required switching to surgery during the first treatment procedure. The reasons for surgical intervention in the remaining [redacted] patients were as follows: Treatment of thrombosis or occlusion after the first procedure, including treatment for thrombosis suspected to have occurred immediately after device implantation in [redacted] patients (17.8%); relationship to heparin-induced thrombocytopenia (HIT) in [redacted] patients (4.2%); infection in [redacted] patients (3.4%); treatment of hematoma at the access site in [redacted] patients (1.7%); treatment of serous pachymeningitis involving the SFA in [redacted] patients (0.8%); and unknown or undetermined in [redacted] patients (2.5%). Not all patients with HIT had a confirmed diagnosis of HIT based on laboratory test results. Some patients were diagnosed with HIT because its possibility could not be ruled out based on available evidence. Patients with HIT who showed no recovery required drug therapy, device removal, etc.

1.A.(4) Performance and safety specifications

The proposed property or performance specifications for Stent Graft are appearance, circumference strength, radial force, MRI safety, heparin activity, longitudinal tensile strength, erosion resistance, deployment precision, flexibility, long-term durability (pulsating fatigue test and complex load test), and radiopacity. Those proposed for Catheter are the tensile strength at the catheter junctions (dual lumen tube - hub, dual lumen tube - end shaft, and end tip - end shaft) and leakage tolerance. Those for the

entire delivery system are appearance, delivery system deployment strength, accessary compatibility, deployment reliability, and radiopacity. The proposed safety specifications for Gore Viabahn Stent Graft are biological safety and bacterial endotoxins, as well as the sterility assurance and concentration of residual ethylene oxide in the manufacturing process. As described later in Sections 2 to 5, Gore Viabahn Stent Graft conformed to all of the proposed specifications.

1.B Outline of the review conducted by PMDA

PMDA asked the applicant to add a specification regarding the permeability of the graft of Stent Graft because it is an important feature.

The applicant's explanation:
A specification of "water permeability" would be added with reference to the results of the "water entry pressure test" submitted as the data supporting the physicochemical properties of Gore Viabahn Stent Graft.

PMDA reviewed the added specification and the data regarding the setting of specifications, including "2. Physicochemical properties" described later, and concluded that there was no particular problem with the tests, methods, and acceptance criteria proposed as the performance and safety specifications.

2. Design and Development

2.A Summary of the data submitted

2.(1) Physicochemical properties (Attached document 2-1[1]-1 to 2-1[1]-47)

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

In addition to the data from the tests included in the proposed performance and safety specifications, the applicant submitted the data with the delivery system from a tensile strength test between the deployment line and the knob, stent graft diameter measurement test, and stent graft migration resistance test, as well as the data with Stent Graft from a stent graft water permeability test, stent graft fibril length measurement in the PTFE molecular structure, material analysis and mechanical characteristics of nitinol, finite element analysis that tested the occurrence of distortion under load conditions (pulsation, bend, axial compression, and kink), and water permeability test at the stent graft junctions that tested the leakage at the junction between the stent grafts and between the stent graft and a mock blood vessel.

The data from tests for which specification limits have been established demonstrated that Gore Viabahn Stent Graft met the proposed respective specification limits for the tests. The applicant explained that attributes in which tests were not included in the performance and safety specifications could be assured by the specifications of shape, structure, raw materials, and others.

The test results submitted were from the tests using Gore Viabahn Stent Graft. The proposed specifications for Gore Viabahn Stent Graft were established by referring to the test results of the artificial blood vessels, stents, etc. of the previous generation product and approved products, except for the test at the delivery catheter junctions in which specifications were determined in compliance with applicable ISO standards. The applicant also explained the appropriateness of setting the specifications for Gore Viabahn Stent Graft based on the test results of the previous generation product and approved products.

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

PMDA asked the applicant about measures to prevent the end tip from detaching from the catheter as observed in a mock use test of the delivery system and the occurrence of this malfunction after those measures were taken.

The applicant's explanation:
The mock use test of the delivery system was conducted using 14 catheters with the 13 mm diameter stent graft placed. The detachment of the end tip was found in 1 test catheter when it was removed from the introducer sheath. The confirmed cause of this malfunction was the operating instructions for test sample manufacturing included no instruction about the adhesion of the end tip to the catheter, which resulted in the test catheters manufactured without correct machine settings. To improve the situation, detailed operating instructions about the adhesion of the end tip were prepared. There has been no report, etc. on malfunctions likely due to the poor adhesion of the end tip in the manufacturing process. No device malfunctions, including the detachment of the end tip, were reported in the Japanese clinical study of Gore Viabahn Stent Graft.

PMDA's view:
For the following reasons, PMDA accepted the submitted data on the physicochemical properties: The updated operating instructions ensure the uniform control of the adhesion process of the end tip, and neither detachment of the end tip nor malfunctions in the clinical study because of a similar manufacturing problem have been reported since the update; the strength of the end tip was also measured in the strength test at the delivery catheter junctions, which demonstrated the conformance of the end tip to the specification limits; sampling tests will be performed in the actual manufacturing process; and no similar event was reported in the clinical study conducted for this application.

2.(2) Biological safety (Attached document 2-1[2]-1 to 2-1[2]-14)

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

To support the biological safety of Gore Viabahn Stent Graft, the applicant submitted the data from the performance and safety specification tests.

The delivery catheter, a medical device that comes into short contact with the circulating blood, was tested for cytotoxicity, sensitization, irritability/intradermal reaction, acute systemic toxicity, pyrogenicity, and blood compatibility for Catheters A and C, and bacterial endotoxins for Catheter A. Catheter B is made of the same raw materials as Catheter A, except for the end tip which is made of the same raw materials (for the part that comes into contact with blood) as the delivery catheter of the applicant's approved product "Excluder Bifurcated Stent Graft System" (Approval number 21900BZY00011000), and the above tests for Catheter B were not conducted.

The raw materials of the graft, adhesive tapes, and heparin-bonding layer are the same as those of the applicant's approved product "Gore Propaten Vascular Graft" (Approval number 22500BZX00324000) (hereinafter referred to as Propaten), and the tests for the graft, adhesive tapes, and heparin-bonding layer were omitted. The raw materials of the stent wire are the same as those of "Excluder Bifurcated Stent Graft System," and the tests for the stent wire are also omitted.

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

PMDA reviewed the submitted data and concluded that there was no particular problem with the biological safety of Gore Viabahn Stent Graft.

2.(3) Stability and durability (Attached document 2-1[3]-1 to 2-1[3]-4)

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

As described in 2.(2) Biological safety, the graft, adhesive tapes, heparin-bonding layer, and stent wire of Stent Graft are made of the same raw materials as the applicant's approved products. The radiopaque markers are made of the same raw materials as "Excluder Bifurcated Stent Graft System" and "Gore-

Tex Artificial Dura Mater II" (Approval number 21300BZY00693000). The applicant submitted the data from the heparin activity test of Stent Graft samples stored in real time for 3 years supporting the stability of Gore Viabahn Stent Graft. Stent Graft met the specifications.

To support the stability of the delivery system, the applicant submitted the data from the stability study of Catheters A to C that had been stored in real time for 3 years in the tests for the performance and safety specifications. Catheter B is made of the same raw materials as Catheter A. Catheter C has a hub made of the same raw materials and the same adhesive as Catheter A, and a dual lumen tube made of the same raw materials as "Excluder Bifurcated Stent Graft System." For these reasons, the leakage test of the catheters and the strength test at the dual lumen tube-hub junction were not conducted.

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

PMDA reviewed the submitted data and concluded that there was no particular problem with the stability of Gore Viabahn Stent Graft. The durability of Stent Graft was assessed in the long-term durability tests (pulsating fatigue test and complex load test) and by finite element analysis, which are included in the performance and safety specifications in 2.(1) Physiochemical properties, showing no particular problem.

2.(4) Performance (Attached document 2-1[4]-1 to 2-1[4]-5)

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

The applicant submitted the following performance data.

Acute implantation test

An acute implantation test in dogs and sheep was conducted. The tests used samples of Gore Viabahn Stent Graft (including the model without heparin-bonding) having different diameters of Stent Graft, Catheter, and compatible guidewires, and with or without radiopaque markers. Each test sample was placed in the abdominal branching arteries (renal, superior mesenteric, hepatic, and splenic arteries), iliac artery, and femoral artery of each animal to assess flushing performance, compatibility with concomitant medical devices, trackability, pushability, radiopacity, deployment performance (deployment and implantation), deployment precision, catheter removal, and vascular injury (e.g., perforation and dissection). The test showed no particularly significant event.

Long-term implantation test

One test sample each of Hemobahn 5.0 mm in diameter (12 samples in total) was placed in healthy blood vessels of the bilateral common iliac arteries or SFAs of 6 dogs to assess the performance (trackability, pushability, pliability, conformability, device visibility on radiographs, catheter visibility on radiographs, deployment precision, recovery of delivery catheter, and compatibility with concomitant medical devices), functionality (structural integrity, conformability, effects of a balloon, blood inflow/outflow, sealing capability, migration resistance, durability, flexibility, and wrinkles/grooves of graft), 30- and 90-day clinical and histopathological safety, and vascular patency of the delivery system/stent graft.

The performance and functionality tests of the delivery system/stent graft showed the poor performance in 1 of the 12 test samples in terms of deployment precision, catheter recovery, and migration resistance. The catheter was recovered without any problem. The stent graft was deployed and implanted at a site 7 to 8 mm from the target site without any problem. This device maintained vascular patency 90 days after implantation without a trace of migration. Overall, the functionality of the device was satisfactory. The other test samples showed no particular problem.

The vascular patency assessment showed the maximum stenosis rate of 0% to 27.73% in the 6 stent grafts in the 30-day observation group, and 9.94% to 45.69% in the 6 stent grafts in the 90-day observation group. The test sample having the highest stenosis rate had a fibrin thrombus on the luminal surface as identified by microscopy.

Microscopic histology of 4 of the 6 test samples in the 30-day observation group showed the almost endothelialized luminal surface of each stent graft with very little inflammatory reaction. Scanning Electron Microscopy (SEM) of the remaining 2 of the 6 test samples revealed 1 test sample widely covered by the neointima including endothelial cells and the remaining 1 test sample partially (but not completely) covered by the neointima including endothelial cells. Microscopy of 4 of the 6 test samples in the 90-day observation group showed the patency of all test samples with mild inflammatory reaction, except for 1 stent graft whose distal lumen was narrowed by the neointima. SEM of the remaining 2 of the 6 test samples revealed the complete integration of both stent grafts into the vessel walls with endothelialization. In this test, antiplatelet therapy with aspirin 325 mg/day and dipyridamole 50 mg/day was started ≥3 days before the procedure and continued throughout the entire survival period.

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

As shown in Table 3, the stent grafts of Hemobahn, the test sample for the long-term implantation test, and Gore Viabahn Stent Graft have some differences, including the secondary fiber helix, methods of mounting and deployment, heparin-bonding layer, and wavy shape of stent graft end. PMDA asked the applicant to explain the effects of these differences between Hemobahn and Gore Viabahn Stent Graft on its long-term safety.

The applicant's explanation:

The performance and functionality of the delivery system and stent graft of Gore Viabahn Stent Graft after the design change were evaluated in the acute implantation test, showing its good deployment performance. Table 5 shows the effect of the differences in the stent graft structure in a long-term safety, and the differences in the stent graft structure will not affect the long-term safety of Gore Viabahn Stent Graft.

Table 5. Effects of the differences between Gore Viabahn Stent Graft and Hemobahn in animal test

	Gore Viabahn Stent Graft	Hemobahn	Effect of difference
Secondary fiber helix [redacted]	No	Yes	Secondary fiber helix [redacted]. Therefore, the secondary fiber helix will not affect the vascular patency after the deployment of the stent graft of Hemobahn.
Heparin-bonding layer	Yes	No	A 180-day implantation test of Propaten in dogs with the same heparin-bonding layer as that of Gore Viabahn Stent Graft was conducted to compare the vascular patency and tissue reaction between the grafts with and without a heparin-bonding layer. Propaten had a superior patency to the graft without a heparin-bonding layer and caused no adverse event attributable to the heparin-bonding layer. These results suggested the long-term safety of Gore Viabahn Stent Graft.
Wavy shape of stent graft end (at the proximal end of the delivery catheter)	Yes	No	The graft is cut in waves to fit with the shape of the stent strut at the graft end. No change is made to the stent strut. This [redacted].

One of the 3 animals in the 90-day observation group had stenosis likely due to thrombus. PMDA also asked the applicant to discuss the long-term safety of Gore Viabahn Stent Graft.

The applicant's explanation:
The results of the animal study of Propaten submitted as reference data verified that the vascular patency of the product with the heparin-bonding layer was superior to that of the product without the heparin-bonding layer at 180 days after implantation, suggesting that Gore Viabahn Stent Graft will not be associated with a higher incidence of stenosis than Hemobahn. On the other hand, literature references[5-6][7][8] report that dogs are more susceptible to thrombosis than humans. Therefore, there are certain limitations in extrapolating the data from animal studies into humans. Taking into consideration the results of the clinical study, etc., the incidence of stenosis caused by Gore Viabahn Stent Graft in the clinical study can be acceptable.

PMDA's view:
The performance test was conducted in dog and sheep models. The blood stream in the animal artery where Gore Viabahn Stent Graft was implanted does not largely differ from that in humans. These animal species are widely used in assessment of endovascular treatment devices. Given this, it is reasonable to evaluate Gore Viabahn Stent Graft using these animal models.

The acute implantation test was intended to evaluate the implantation and delivery performance of Gore Viabahn Stent Graft in vascular injury treatment and vascular patency treatment. The implantation and delivery performance of Gore Viabahn Stent Graft, and the post-procedural vascular injuries in vascular injury treatment were investigated in the abdominal blood vessels and iliac artery, where stent implantation or delivery is more difficult among the blood vessels for which Gore Viabahn Stent Graft is expected to be indicated, as well as the carotid artery. Gore Viabahn Stent Graft was also assessed in the femoral artery in the same manner in the vascular patency treatment. Therefore, the acute efficacy and safety of Gore Viabahn Stent Graft are assured.

The applicant's explanation that Hemobahn, whose stent graft has a different structure from Gore Viabahn Stent Graft, should be regarded as the worst case in terms of the incidence of occlusive events in the long-term implantation test is acceptable. On the other hand, the effect of the heparin-bonding layer on endothelialization has not been fully discussed yet. Whether the heparin-bonding layer delays endothelialization remains unclear. The duration of antiplatelet therapy, etc. should be determined with reference to the results of the clinical study.

On the basis of these discussions, PMDA accepted the performance data of Gore Viabahn Stent Graft.

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 Gore Viabahn Stent Graft 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 Ministerial Announcement No. 122, 2005) and the Ministerial Ordinance on Quality Management System for Medical Devices and *In Vitro* Diagnostics (MHLW Ministerial Ordinance No.169, 2004).

3.B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with the conformity of Gore Viabahn Stent Graft to the Essential Principles.

4. Risk Management

4.A Summary of the data submitted

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

4.B Outline of the review conducted by PMDA

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

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on manufacturing process and site, sterilization (ethylene oxide gas sterilization and ethylene oxide gas sterilization residual test), and quality control. Gore Viabahn Stent Graft uses swine heparin sodium, which is purified using the same method as "Propaten" by the same supplier. The heparin sodium has been shown to conform to the "Standards for Biological Ingredients, 4.3 Standards for Animal-derived Materials, dated May 20, 2003."

5.B Outline of the review conducted by PMDA

PMDA reviewed the document on 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.(1) Vascular injury treatment (Attached document 6-1)

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

The applicant submitted a clinical evaluation report prepared based on the results of literature search on vascular injury treatment of arteries in the chest, abdomen, or pelvic, excluding the aorta, coronary artery, brachiocephalic artery, carotid artery, vertebral artery, and pulmonary artery, with Gore Viabahn Stent Graft or its previous generation Hemobahn.

Table 6 outlines the method of the literature search conducted by the applicant. Of 279 reports found through the literature search, reports were excluded if they did not report vascular injury treatment of arteries in the chest, abdomen, or pelvic, excluding the aorta, coronary artery, brachiocephalic artery, carotid artery, vertebral artery, and pulmonary artery, with Gore Viabahn Stent Graft or its previous generation Hemobahn. Reports on the use of Gore Viabahn Stent Graft or Hemobahn in conditions other than vascular injury, reports on the use of these devices in animals, and review reports not detailing individual cases of treatment with Gore Viabahn Stent Graft were also excluded. Twenty-two publications were identified on traumatic or iatrogenic vascular injury treatment of arteries in the chest, abdomen, or pelvic, excluding the aorta, coronary artery, brachiocephalic artery, carotid artery, vertebral artery, and pulmonary artery, with Gore Viabahn Stent Graft or its previous generation Hemobahn.

Table 6. Outline of literature search method

Final date of search	November 4, 2014
Period covered by search	All publications up to the final date of search
Search engine	Embase and MEDLINE
Search keywords ("*" means forward-match)	Viabahn, Hemobahn, Haemobahn, [Gore (within 5 words of) stent*, Gore (within 5 words of) endovasc*, Gore (within 5 words of) endoprosth*, Gore (within 5 words of) intraluminal*] NOT aort* (in title) Gunshot*, trauma*, penetrate*, injur*, combat*, wartime*, war, wars, military*, blunt, iatrogen*, accident*, knife*, motor vehicle*, stab*, emergen*, urgen*, perforat*, rupture (NOT rupture [within 5 words of] aneurysm), pseudoaneurysm (NOT pseudoaneurysm [within 5 words of] dialysis), fistula (NOT fistula [within 5 words of] dialysis
Search method	The database of the search engines was accessed for literature search.
Literature selection criteria	• Publications must be about Gore Viabahn Stent Graft or Hemobahn (former name of Gore Viabahn Stent Graft), • not be about animal or *in vitro* studies, • have been peer-reviewed, • be written in English, • report the use of Gore Viabahn Stent Graft or Hemobahn in vascular injury treatment of arteries that meet the anatomical requirements of Gore Viabahn Stent Graft in the chest, abdomen, or pelvic, excluding the aorta, coronary artery, brachiocephalic artery, carotid artery, vertebral artery, and pulmonary artery, • not be review reports, excluding those detailing individual cases of unprecedented treatment with Gore Viabahn Stent Graft, and • be about treatment of traumatic or iatrogenic vascular injury.
Search refinement	Extracted publications were reviewed and those that did not meet the above selection criteria were excluded.

Table 7. List of 22 publications used in clinical evaluation of vascular injury treatment

Number	Author, title, source
1	Bartorelli AL., et. al. Endovascular Repair of Iatrogenic Subclavian Artery Perforations Using the Hemobahn Stent-graft. *Journal of Endovascular Therapy.* 2001;8(4):417-421.
2	Rivellini C., et. al. Endovascular technique as therapy of choice in complicated Port-a-Cath catheter use. *Giornale Italiano di Chirurgia Vascolare.* 2002;1:389-399.
3	Schoder M., et. al. Elective and Emergent Endovascular Treatment of Subclavian Artery Aneurysms and Injuries. *Journal of Endovascular Therapy.* 2003;10(1):58-65.
4	Pancharatnam D., et. al. Delayed Presentation of a Post-Traumatic Subclavian Pseudoaneurysm. *Vascular Disease Management.* 2007;4(6):171-173.
5	Ewings E.L., et. al. Prolonged success with a covered endovascular stent after emergent use in radiation-induced subclavian artery blowout: A case report. *Vascular and Endovascular Surgery.* 2008;1:187-191.
6	Derom A., et. al. Endovascular Treatment of Acute Subclavian Pseudo-aneurysm after Fracture of the Clavicle. *Acta Chirurgica Belgica.* 2008;108.
7	Aarvold A., et. al. Arterio-ureteric Fistula Following Iliac Angioplasty. C*ardiovascular and Interventional Radiology.* 2008;31:821-823.
8	Abi-Jaoudeh N., et. al. Management of Subclavian Arterial Injuries Following Inadvertent Arterial Puncture During Central Venous Catheter Placement. *Journal of Vascular and Interventional Radiology.* 2009;20:396-402.
9	Ziporin S.J., et. al. A case of external iliac arteriovenous fistula and high-output cardiac failure after endovenous laser treatment of great saphenous vein. *Journal of Vascular Surgery.* 2010;1:715-719.
10	Momtahen M., et. al. Peripheral arteriovenous fistula after coronary stenting. *Texas Heart Institute Journal.* 2010;19:121-122.
11	O'Connor D.J., et. al. Endovascular management of multiple arteriovenous fistulae following failed laser-assisted pacemaker lead extraction. *Journal of Vascular Surgery.* 2010;1:1517-1520.
12	Goltz J.P., et. al. Emergency and elective implantation of covered stent systems in iatrogenic arterial injuries. *RoFo Fortschritte auf dem Gebiet der Rontgenstrahlen und der Bildgebenden Verfahren.* 2011;22:618-630.
13	Canaud L., et. al. Endovascular repair of aorto-iliac artery injuries after lumbar-spine surgery. *Journal of Vascular Surgery.* 2011;1:584.
14	Gilani R., et. al. Overcoming challenges of endovascular treatment of complex subclavian and axillary artery injuries in hypotensive patients. *Journal of Trauma and Acute Care Surgery.* 2012;1:771-773.
15	Hoffer EK. Endovascular intervention in thoracic arterial trauma. *Injury.* 2008;39:1257-1274.
16	Fudim M., et. al. Peripheral Vascular Complications During Transcatheter Aortic Valve Replacement: Management and Potential Role of Chronic Steroid Use. *Perspectives in Vascular Surgery and Endovascular Therapy.* 2013;2(4):206-209.
17	Rocha L., et. al. Endovascular Approach for Peripheral Arterial Injuries. *Annals of Vascular Surgery.* 2013;27(5):587-593.
18	Andrade A., et. al. Brachiocephalic artery & subclavian vein injury with embolization to the pulmonary vasculature. *Journal of Pediac Surgery Case Reports.* 2014;2:394-396.
19	Nadeau-Routhier C., et. al. Iatrogenic extra-pleural haematoma following cardiac device implantation. *Europace.* 2014;16(11):1673.
20	Wheatcroft MD., et. al. Two cases of arteriovenous fistula formation between the external iliac vessels following endovenous laser therapy. *Vascular.* 2014;22(6):464-467.
21	Wallace MJ., et. al. Superior Mesenteric Artery Pseudoaneurysm Following Pancreaticoduodenectomy: Management by endovascular stent-graft placement and transluminal thrombin injection. *Cardiovascular Interventional Radiology.* 2007;30:518-522.
22	Kaw LL Jr., et. al. Use of a Stent Graft for Bleeding Hepatic Artery Pseudoaneurysm Following Pancreaticoduodenectomy. *Asian Journal of Surgery.* 2006;29(4):283-286.

Table 8. Summary of the publications used in clinical evaluation of vascular injury treatment

Publication	Classification, application site, No. of patients	Device	Primary hemostasis	Adverse event	Outcome/summary
1	Iatrogenic, subclavian artery, 2	#1:Hemobahn #2:Hemobahn	Successful	—	Experience in treatment with Hemobahn in 2 patients with iatrogenic vascular injury to the subclavian artery was reported. Month 10 and 12 follow-up showed no symptoms indicating occlusion, migration, deformity, or fracture.
2	Iatrogenic, subclavian artery, 1	Hemobahn	Successful	—	Hemobahn was implanted to treat iatrogenic vessel perforation in the subclavian artery caused by implantation of the central venous catheter. The patient had a good postoperative outcome.
3	Iatrogenic, subclavian artery, 7	#1: Hemobahn #2: Hemobahn #3: Hemobahn #4: Hemobahn #5: Jo-stent, Hemobahn #6: Hemobahn #7: Hemobahn	Successful	#3 died from a comorbidity. #4 died from a comorbidity. #5 had a 50% stenosis of a stent graft from another company (Jo-stent) at Month 8 (asymptomatic). #7 died from a comorbidity.	Treatment with the stent graft was successful in all patients who received Hemobahn to treat iatrogenic vessel perforation in the subclavian artery caused by misplacement of the central venous catheter. Subsequently, 3 patients died from comorbidities (chronic obstructive pulmonary disease, lung cancer, and pancreatitis chronic). The remaining 4 patients had a stent graft patency at the time of follow-up.
4	Traumatic, subclavian artery, 1	Hemobahn	Successful	Thrombolysis (urokinase 150,000 units for ≥15 minutes) and embolectomy with a Fogarty catheter were performed to treat occlusion distal to the brachial artery attributable to a large thrombus distal to the subclavian artery that occurred during a surgery and shower emboli that occurred during thrombolysis to treat the large thrombus. The treatments resolved the large thrombus in the subclavian artery. However, the emboli spread and caused occlusion distal to the brachial artery. The blood flow was restored by subsequent embolectomy with a Fogarty catheter.	Case of treatment with Hemobahn in 1 patient with a pseudoaneurysm in the subclavian artery, which was accompanied by a large thrombus caused by a road traffic accident, was reported. Blockage of the pseudoaneurysm with Hemobahn and thrombolytic therapy with urokinase successfully maintained the sensory and motor function of the arm.

Publication	Classification, application site, No. of patients	Device	Primary hemostasis	Adverse event	Outcome/summary
5	Iatrogenic, subclavian artery, 1	Gore Viabahn Stent Graft*[1]	Successful	• Spontaneous hemorrhage (approximately 500 mL) occurred at Month 2 but recovered. • Additional implantation of Gore Viabahn Stent Graft to treat stenosis and pseudoaneurysm distal to Gore Viabahn Stent Graft at Month 2 failed to completely cover the stenosis site. One more set of Gore Viabahn Stent Graft was added to the affected site. • The patient died from terminal cardiac failure.	Case of treatment with Gore Viabahn Stent Graft in 1 patient with a rupture of the subclavian artery after radiotherapy was reported. The patient was at high risk of surgery. Year 2 follow-up confirmed a stent graft patency without hemorrhage.
6	Traumatic, subclavian artery, 1	Gore Viabahn Stent Graft*[1]	Successful	—	Case of treatment with Gore Viabahn Stent Graft, which successfully stopped hemorrhage, in a patient with a pseudoaneurysm in the subclavian artery, which was caused by fracture and could not be treated by 2 thrombin injections, was reported. Month 9 follow-up verified the blockade of the blood flow to the pseudoaneurysm, with the improved paresis of the arm and no stent fracture.
7	Iatrogenic, iliac artery, 1	Gore Viabahn Stent Graft*[1]	Successful	—	Case of successful treatment of a perioperative artery-to-ureter fistula with Gore Viabahn Stent Graft in a patient who underwent angioplasty and stent placement to treat the occlusive external iliac artery was reported. Month 6 follow-up verified that the patient was asymptomatic.
8	Iatrogenic, subclavian artery, 1	Gore Viabahn Stent Graft*[1]	Successful	The patient died from hepatic failure, adult respiratory distress syndrome, and septic shock.	Gore Viabahn Stent Graft was implanted to block a rupture in the right subclavian artery caused by misplacement of the central venous catheter. The vascular injury treatment was successful. On Day 9, however, the patient died from hepatic failure, adult respiratory distress syndrome, and septic shock.
9	Iatrogenic, iliac artery, 1	Two sets of Gore Viabahn Stent Graft*[1]	Successful	—	One case of iliac arteriovenous fistula after laser treatment of the great saphenous vein was reported. The patient had high output cardiac failure because of this fistula. Implantation of Gore Viabahn Stent Graft in the external iliac artery completely resolved the fistula and cardiac failure.

Publication	Classification, application site, No. of patients	Device	Primary hemostasis	Adverse event	Outcome/summary
10	Iatrogenic, iliac artery, 1	Hemobahn, NuMED CP Stent	Successful	—	Hemobahn was deployed to close an arteriovenous fistula that occurred after coronary stent placement. However, the fistula remained open around the implantation site of the stent graft. The surgeon could not use another set of Hemobahn and placed NuMED CP Stent (covered stent) proximal to the original implantation site of Hemobahn, which resolved the fistula. Month 6 follow-up verified the patient's good condition.
11	Iatrogenic, subclavian artery, 1	iCAST,*2 Gore Viabahn Stent Graft*1	Successful	—	Case of treatment with Gore Viabahn Stent Graft in 1 patient with an arteriovenous fistula in the subclavian artery, which occurred after laser failed to remove the leads of the pacemaker, was reported. Another set of Gore Viabahn Stent Graft was used because the patient's symptoms did not completely resolve and another arteriovenous fistula (carotid artery - brachiocephalic vein) was found. Month 6 follow-up verified that Gore Viabahn Stent Graft was appropriately placed without endoleak.
12	Iatrogenic, iliac artery, 1	Hemobahn	Successful	In-stent stenosis <50% (Month 24)	Gore Viabahn Stent Graft was implanted to treat an injury to the external iliac artery that occurred after PTA and stent placement to treat occlusion. A <50% stenosis was observed at Month 24. Subsequently, the lesion completely resolved without complications.
13	Iatrogenic, iliac artery, 1	Gore Viabahn Stent Graft*1	Successful	—	The blood flow to the injured site was blocked without procedure-related complications. All stent grafts were patent at Year 8.7 (median) (range, Year 0.3-13). The authors reported that this procedure was effective, especially in severe cases.
14	Traumatic, subclavian artery, 3	#1: Gore Viabahn Stent Graft*1 #2: Two sets of Gore Viabahn Stent Graft*1 #3: Gore Viabahn Stent Graft*1	Successful	#2: Late graft thrombosis (Month 14) (asymptomatic)	Gore Viabahn Stent Graft was implanted to treat a penetrating injury to the subclavian artery. The technical success rate was 100%. The primary patency rate was 100% at Month 12. One patient had device occlusion at Month 14, but received no additional treatment because the patient was asymptomatic.

Publication	Classification, application site, No. of patients	Device	Primary hemostasis	Adverse event	Outcome/summary
15	Traumatic, subclavian artery, 1	Gore Viabahn Stent Graft*[1]	Successful	—	Case of endovascular treatment of thoracic arterial injuries to the thoracic aorta and great vessels (brachiocephalic, carotid, and subclavian arteries) was reported. This report concluded that Gore Viabahn Stent Graft was a stent graft that can be used for the treatment of great vessels. Gore Viabahn Stent Graft was used to treat an injury to the subclavian artery, caused by a fall from a tree. The final angiography of the patient revealed no endoleak and an anterograde blood flow. This publication reported that the endovascular treatment resulted in as good technical success rate and short-term incidence of complications as surgical treatment, which resulted in stable hemodynamics. It concluded that endovascular treatment of these blood vessels was a reasonable treatment option for patients meeting the anatomical conditions.
16	Iatrogenic, iliac artery, 1	Two sets of Gore Viabahn Stent Graft,*[1] 2 sets of iCAST*[2]	Successful	• Treatment with 2 sets of iCAST*[2] and transfusion (10 packs of RBC and 6 packs of fresh frozen plasma) resolved a persistent leakage of contrast media after implantation of Gore Viabahn Stent Graft. • Multiple acute punctuate lesions (perioperative) • Seizure (postoperative)	An Edwards Sapien valve was successfully placed with a 24 Fr delivery system. However, an iliac artery rupture accompanied by dissection involving the SFA occurred during the removal of the system. First, the common iliac artery was closed with a balloon, followed by closure of the distal aorta with a balloon. Because of active hemorrhage and unstable hemodynamics, endovascular treatment of the traumatic injury was conducted. Double placement of 2 sets of Gore Viabahn Stent Graft failed to stop the hemorrhage, which was resolved by additional implantation of 2 sets of iCAST*[2] (Atrium). The patient's condition was stable at Year 1 follow-up.
17	Iatrogenic, #1 subclavian artery, #2 iliac artery, #3 subclavian artery, 3	#1: Advanta 2 sets of V12,*[3] Gore Viabahn Stent Graft*[1] #2: Gore Viabahn Stent Graft*[1] Sentinol*[4] #3: Hemobahn, Wallgraft	Successful	#1: Surgical bypass resolved motor dysfunction of the arm caused by graft occlusion (Year 2). #3: Conservative treatment of moderate motor dysfunction of the arm caused by graft occlusion (Year 1) was ongoing.	No death, amputation, etc. were reported during the follow-up period (48 months after Day 13). The authors concluded that treatment of penetrating traumatic injuries to arteries with a stent graft(s) was safe and effective.

Publication	Classification, application site, No. of patients	Device	Primary hemostasis	Adverse event	Outcome/summary
18	Traumatic, subclavian artery, 1	Gore Viabahn Stent Graft*1	Successful	• Asymptomatic thyrocervical arterial occlusion due to stent graft placement • After implantation of Gore Viabahn Stent Graft, type I endoleak remained. However, Month 6 follow-up verified its natural resolution.	Angiography of the right subclavian artery on the following day of injury indicated an arteriovenous fistula in the right subclavian artery. Implantation of Gore Viabahn Stent Graft resolved the fistula. However, type I endoleak remained. The type I endoleak was managed conservatively. CT angiography at Month 6 follow-up verified the resolution of the endoleak and fistula. Month 23 follow-up identified no symptom in the patient, with a good stent graft patency as confirmed by ultrasonography.
19	Iatrogenic, subclavian artery, 1	Gore Viabahn Stent Graft*1	Successful	—	Gore Viabahn Stent Graft was implanted to treat a subclavian artery perforation that occurred after implantation of a defibrillator for cardiac resynchronization therapy. No information regarding the results of the implantation or the duration of follow-up was reported.
20	Iatrogenic, iliac artery, 1	Gore Viabahn Stent Graft*1	Successful	Slight leakage of lymph from the access site	Gore Viabahn Stent Graft was implanted to close an external iliac arteriovenous fistula that occurred after venous laser treatment. Month 12 follow-up verified the stent graft patency and the absence of the fistula.
21	Iatrogenic, superior mesenteric artery, 1	Gore Viabahn Stent Graft*1	Secondary hemostasis was required because of unsuccess-ful hemostasis	• A pseudoaneurysm in the right hepatic artery accompanied by nausea, vomiting, and gastrointestinal haemorrhage was resolved by transfusion, a microcatheter, and microcoil embolism. • The retrograde blood flow to the pseudoaneurysm that received the initial treatment via the jejunum - jejunum collateral circulation was resolved by injection of 500 units of bovine thrombin into the pseudoaneurysm and embolism at the origin of the second jejunal artery with a 5 mm microcoil. • The patient died from advanced pancreatic adenocarcinoma.	Pancreatic head was resected to treat pancreatic adenocarcinoma. Angiography on Day 64 showed a pseudoaneurysm originating from the proximal superior mesenteric artery, which was treated by placement of Gore Viabahn Stent Graft. After implantation of Gore Viabahn Stent Graft, no residual leakage was found around the graft. However, CT on Day 2 showed a residual leakage. This leakage was caused by the retrograde blood flow to the pseudoaneurysm via the jejunum - jejunum collateral circulation. The retrograde blood flow was treated by thrombin injection and coil embolization. Five days later, a new pseudoaneurysm was found in the right hepatic artery, which was treated by coil embolization. The patient died from advanced pancreatic adenocarcinoma approximately 2 months later.

Publication	Classification, application site, No. of patients	Device	Primary hemostasis	Adverse event	Outcome/summary
22	Iatrogenic, hepatic artery, 1	Two sets of Gore Viabahn Stent Graft*1	Successful	• Asymptomatic occlusion of the left hepatic arterial bifurcation due to stent graft placement • Liver abscess involving the left lobe and caudate lobe was resolved by percutaneous catheter drainage at Week 5.	The patient experienced melaena and twilight state 3 weeks after pancreatic head resection to treat distal common choledochal adenocarcinoma. Abdominal angiography showed a large pseudoaneurysm involving the main hepatic artery. The pseudoaneurysm was treated with Gore Viabahn Stent Graft, with a slight distal endoleak remaining. The endoleak was resolved by additional implantation of the second set of Gore Viabahn Stent Graft. The left hepatic arterial bifurcation was occluded with a stent graft. Month 8 follow-up revealed no gastrointestinal haemorrhage.

*1: Including devices without heparin-bonding layer
*2: iCast Covered Stent System (Atrium Medical)
*3: The brand name of Advanta V12 in the US is iCast Covered Stent System.
*4: Sentinol (Boston Scientific)

6.(1).A.1) Sizes used

Table 9 shows the device sizes used in the publications shown in Tables 7 and 8.

Table 9. Number of devices by size

		Diameter (mm)										Total
		5	6	7	8	9	10	11	12	13	Unknown	
Length (cm)	2.5	1	1	0	1*		0	0		0	0	3
	5	0	3	2	5	4	4	2		1	0	21
	10	0	0	0	5	0	2	0		1	1	9
	15	0	0	0	0	0	0				0	0
	Unknown	0	0	0	1	0	0	1***	1**	0	1****	4
Total		1	4	2	12	4	6	3	1	2	2	37

Number of Gore Viabahn Stent Graft sets or Hemobahn sets. Devices in slashed columns do not exist.

* The reported size was 8 mm × 2 cm, but the actual size must have been 8 mm × 2.5 cm because a device 2 cm in length does not exist.

** The reported diameter was 12 mm, but it must be incorrect because a device 12 mm in diameter does not exist.

*** The diameter must have been 11 mm because an 11 Fr sheath was used. The actual diameter is not clearly described.

**** The mean calculated in the publication included the sizes of devices of other companies.

6.(1).A.2) Target diseases, target sites, and patient characteristics

Literature search found that the injury sites were the subclavian artery in 23 patients, iliac artery in 8 patients, superior mesenteric artery in 1 patient, and hepatic artery in 1 patient. The treated injuries included pseudoaneurysm, fistula, and arterial injuries. Among patients whose sex was reported in publications, 11 men and 14 women had iatrogenic vascular injuries, and 6 men and 1 woman had traumatic vascular injuries. On the basis of the data from publications that reported the age of individual patients, the mean age was 59.2 ± 14.6 years (n = 25) for patients with iatrogenic vascular injuries, 47.9 ± 28.9 years (n = 7) for patients with traumatic vascular injuries, and 56.7 ± 18.7 years (n = 32) overall. The most common previous illness reported in publications (n = 25) was cardiovascular disease in 8 patients, followed by cerebrovascular disease and lung disease in 3 patients each, hypertension, peripheral vascular disease, and obesity in 2 patients each, and diabetes mellitus, renal disease, and smoking in 1 patient each.

6.(1).A.3) Efficacy of Gore Viabahn Stent Graft

6.(1).A.3).(a) Hemostatic performance

For this assessment, “primary hemostasis” was defined as hemostasis that was achieved by appropriately sealing the target injury prior to closure of the access site. Accordingly, hemostasis that was achieved by using an additional device(s) during the procedure was also regarded as primary hemostasis as long as it occurred prior to closure of the access site. “Secondary hemostasis” was defined as hemostasis that was achieved by accessing the injury site again after the closure of the access site during the initial treatment.

Hemostasis was considered successful when a publication explicitly or implicitly reported the “successful hemostasis.” Hemostasis was considered unsuccessful only when a publication reported “hemostasis failure.” Fifteen publications (16 patients) clearly reported successful hemostasis, while 7 publications (16 patients) did not clearly state successful hemostasis.

As a result of the literature research, all patients achieved primary hemostasis, except for 1 patient with an iatrogenic injury to the superior mesenteric artery who underwent coil embolization for the retrograde blood flow to a pseudoaneurysm via the collateral circulation. The primary hemostasis rate was 97.0% (32 of 33 patients). Of these, 10 patients received implantation of multiple devices, including those from other companies. All of them achieved primary hemostasis. No patient required additional treatment for hemostasis after implantation of Gore Viabahn Stent Graft, other than the 1 patient who failed to achieve primary hemostasis.

6.(1).A.3).(b) Endoleak

Endoleak was considered absent when a publication explicitly reported no occurrence of endoleak or did not mention the occurrence of endoleak at all. Only when a publication explicitly reported the occurrence of endoleak was it considered that endoleak was present. Endoleak was absent in 4 patients, while the event was not reported in 27 patients.

Two publications reported the occurrence of endoleak in 2 patients. One of these patients (Literature No. 18) received Gore Viabahn Stent Graft for the treatment of a traumatic injury to the subclavian artery, with a type I endoleak. Month 6 follow-up verified the resolution of the endoleak. The remaining 1 patient (Literature No. 21) received Gore Viabahn Stent Graft for the treatment of an iatrogenic injury to the superior mesenteric artery. The publication reported the retrograde blood flow to a pseudoaneurysm via the second jejunum artery – third jejunum artery collateral circulation. From this information, the presence of a type II endoleak was assumed. This event was considered not associated with the function of Gore Viabahn Stent Graft.

No publication reported stent graft integrity or migration.

6.(1).A.3).(c) Long-term results

Publications providing information on a follow-up period were used to assess the duration of follow-up. Table 10 shows the number of patients per follow-up timeframe. Five publications followed up 6 patients for ≥1 year after procedures. All of these patients had a stent patency.

Table 10. Duration of follow-up (22 publications, 33 patients)

	Iatrogenic vascular injury (number of patients)	Traumatic vascular injury (number of patients)	Total (number of patients)
≤30 days	4	0	4
≥31 days and <1 year	12	2	14
≥1 year	5	1	6
Unknown or not identified	5	4	9
Total	26	7	33

6.(1).A.4) Safety of Gore Viabahn Stent Graft

6.(1).A.4).(a) Adverse event

A total of 27 adverse events were reported in 16 patients. Of the 27 adverse events, 2 events were definitely related to Gore Viabahn Stent Graft and 10 events were possibly related to Gore Viabahn Stent Graft. Table 11 shows the number of adverse events and the details.

Table 11. Adverse events definitely or possibly related to Gore Viabahn Stent Graft

	Iatrogenic vascular injury (number of events)	Traumatic vascular injury (number of events)	Total (number of events)
Lymph leakage from the access site	1	0	1
Graft occlusion	2	0	2
Pseudoaneurysm	1	0	1
Stenosis	2	0	2
Thrombosis	0	1	1
Thromboembolism	0	1	1
Contrast media leakage*	1	0	1
Occlusion of collateral vessel	1	1	2
Type I endoleak	0	1	1
Total	8	4	12

* Persistent leakage of contrast media after implantation of Gore Viabahn Stent Graft. Perioperative placement of a device manufactured by another company resolved the leakage.

6.(1).A.4).(b) Additional treatment for unsuccessful hemostasis after treatment with Stent Graft alone

Of the patients reported in these publications, 10 patients required placement of multiple stent grafts. Of them, 3 patients received multiple sets of Stent Graft. The remaining 7 patients received Stent Graft in combination with BMSs, covered stents, balloon catheters, etc. from other companies. All patients achieved hemostasis. Of the 7 patients who failed to achieve hemostasis with Gore Viabahn Stent Graft alone, 3 patients failed to achieve hemostasis with other company's device, including "Graft Master (Jo-stent)" and "iCast Covered Stent System," but successfully achieved hemostasis with Gore Viabahn Stent Graft. The remaining 4 patients failed to achieve hemostasis with Stent Graft and successfully achieved hemostasis with other companies' devices not approved in Japan.

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

6.(1).B.1) Clinical positioning and appropriateness of clinical evaluation of Gore Viabahn Stent Graft based on publications

The Needs Study Group clarified that the primary purpose of traumatic vascular injury treatment is immediate life-saving and reported the high usefulness of endovascular stent grafts in that these devices are low invasive and can treat lesions without aggravating hemorrhage from other injured sites. The group also stressed "the importance of immediate treatment of iatrogenic vascular injuries because they often require emergent intervention." Graft Master, which is used to treat perforation in the coronary artery or saphenous vein, and Gore CTAG Thoracic Endoprosthesis, which is used for traumatic injuries to the thoracic aorta, are approved in Japan as stent grafts for the treatment of traumatic or iatrogenic vascular injuries. No stent graft for peripheral vascular injuries is approved in Japan. PMDA asked the applicant to explain the medical needs and clinical positioning of Gore Viabahn Stent Graft in the treatment of peripheral vascular injuries.

The applicant's explanation:
Vascular injuries in the subclavian, iliac, renal, splenic, celiac, and other arteries can be caused by iatrogenic vascular injuries associated with endovascular treatments, such as drainage for the treatment of obstructive jaundice and reservoir catheter placement for anticancer treatment, and traffic accidents, etc. Currently, embolization materials such as coils are used to achieve hemostasis in some cases. Because of the importance of treatment to secure the blood flow to the organs, however, many publications[9-10,11,12,13,14,15,16,17,18,19,20] have reported the off-label use of conventional stent grafts (e.g., coronary stent grafts and covered stents for the bile duct) in Japan. Given these points, there appears to be medical needs for Gore Viabahn Stent Graft. In Europe, Gore Viabahn Stent Graft was approved in 1996 for indications including vascular injuries as a "use of stent graft for peripheral arteries." Gore Viabahn Stent Graft has been used for approximately 20 years.

PMDA's view:
Hemostasis is often difficult to achieve in traumatic and iatrogenic vascular injuries to the subclavian, iliac, celiac, and other arteries. Immediate hemostasis, even temporary hemostasis, can lead to the next possibly life-saving treatments. Current coil embolization, etc. may not always provide hemostasis depending on vascular diameters and lesion sites. For these reasons, Gore Viabahn Stent Graft, which offers another treatment option as a life-saving device, is of great clinical significance.

For vascular injury treatment, Gore Viabahn Stent Graft must (a) be accurately placed at the target site, (b) remain at the implantation site and prevent the blood leakage from the vascular injury site; and (c) have a necessary durability as an implantable medical device. To confirm that Gore Viabahn Stent Graft has these performances to achieve temporary hemostasis, evaluation based on clinical data is required.

However, the feasibility of clinical studies in vascular injuries is low. In Japan, there are high medical needs for stent grafts for peripheral vascular injuries because no such stent graft is available. Gore Viabahn Stent Graft, which is positioned as a life-saving device, will provide great benefits. Some stent grafts are already approved for vascular injuries at different sites. The efficacy of Gore Viabahn Stent Graft can be evaluated based on delivery and sealing performance data from nonclinical studies and publications. The overall evaluation of the efficacy and safety of Gore Viabahn Stent Graft is acceptable provided that literature data demonstrate its successful placement at target sites in peripheral blood vessels and subsequent successful hemostasis.

In the Needs Study Group, treatment of "aneurysms in the iliac and femoropopliteal arteries" was included in the indications of Gore Viabahn Stent Graft. However, peripheral true aneurysms are not immediately life-threatening unlike vascular injuries. Taken together with the comments from the Expert Discussion, the usefulness of Gore Viabahn Stent Graft in the above treatment should be evaluated based on prospective clinical data in comparison with the current standard treatments. The applicant explained that [redacted]. Pseudoaneurysms occur in association with vascular injuries and they should be included in this application. No publication reporting the treatment with Gore Viabahn Stent Graft, 15 cm in length was identified.

The applicant's explanation:
Transection and pull-out of the iliac artery during the use of a large sheath in endovascular treatment of thoracic aortic aneurysms, abdominal aortic aneurysms, etc., and in transcatheter aortic valve treatment were reported. In the case of complete pull-out of the iliac artery, a long device, namely 15 cm, may be required. Gore Viabahn Stent Graft provides a mechanical compression against the vessel wall to stop bleeding. Since hemostasis can be achieved by selecting an appropriate size, a particular stent length or size will not be associated with the increased incidence of adverse events.

PMDA accepted these explanations.

The applicant also explained that the 25 cm length device was not included in the indication of vascular injury treatment because no blood vessel can accommodate the 25 cm device in its anatomical structure.

6.(1).B.2) Efficacy and safety of Gore Viabahn Stent Graft

PMDA asked the applicant to explain the following concerns about the efficacy of Gore Viabahn Stent Graft: (a) Poor hemostasis because of endoleak and (b) poor hemostasis with Gore Viabahn Stent Graft alone.

The applicant's response:

(a) The sealing performance of Gore Viabahn Stent Graft was assessed in nonclinical tests (stent graft water permeability test and water permeability test at the stent graft junctions). In these tests, a water leakage from the graft wall when pressure was put on Gore Viabahn Stent Graft, that when Gore Viabahn Stent Graft was placed in mock blood vessels, and that when multiple devices were placed at the same sites were measured. The tests confirmed that the level of water leakage was acceptable. Gore Viabahn Stent Graft has long been used in clinical practice. It is used for the treatment of traumatic or iatrogenic vascular injuries and other indications. W. L. Gore & Associates, Inc. (US) has collected post-marketing adverse event data of all devices marketed by the company, regardless of their indications. The incidence of endoleak is very low (reported endoleak cases, [redacted]; number of sales, [redacted]; incidence, 0.010%). The reported malfunctions included cases where no complete sealing is required (e.g., securing the blood flow to collateral blood vessels during the treatment of abdominal aortic aneurysms). The incidence reported is, therefore, somewhat

conservative. If a device capable of hemostasis at lesions where surgical access is difficult becomes available for traumatic or iatrogenic vascular injury treatment, it will provide benefits that outweigh the risk of endoleak. The endoleak reported in Literature No. 21 was the retrograde blood flow to a pseudoaneurysm via the collateral circulation. Although implantation of Gore Viabahn Stent Graft alone failed to provide primary hemostasis, the combination use of Gore Viabahn Stent Graft and coil embolization resulted in primary hemostasis.

(b) Twenty-one patients achieved hemostasis with implantation of Gore Viabahn Stent Graft or Hemobahn alone. As described above, 10 patients received multiple stents. In the treatment of traumatic or iatrogenic vascular injuries, hemostasis is not necessarily completed as planned because of their nature. Nevertheless, the usefulness of Gore Viabahn Stent Graft can be evaluated since implantation of Gore Viabahn Stent Graft alone provided a certain level of hemostasis.

PMDA's view:
Only a limited number of patients (n = 33) were evaluated in the clinical evaluation report. According to the publications, 32 patients (97.0%) achieved primary hemostasis, including patients who required additional treatment. However, the actual hemostasis success rate can be lower than the reported figure due to publication bias. PMDA conducted review, taking account of such fact. On the other hand, it is unrealistic to treat all vascular injuries with Stent Graft alone because the conditions of injuries, such as site and severity, vary among cases. The submitted clinical evaluation report identified successful hemostasis cases. The clinical experience and nonclinical results with Stent Graft, including similar medical devices, in vascular injury treatment show the clinical efficacy of Gore Viabahn Stent Graft in hemostasis to a certain extent. Considering that there is currently no approved stent graft for peripheral blood vessels, it is of clinical significance to provide healthcare professionals with this emergency device as a new option. However, the publications included no details of the delivery capability of Gore Viabahn Stent Graft to injured sites, with a very limited number of patients. Endoleak or placement of Gore Viabahn Stent Graft alone may result in unsuccessful hemostasis. Given these points, the intended use of Gore Viabahn Stent Graft should be "Emergency treatment of patients who have blood leakage that is difficult to manage due to a traumatic or iatrogenic vascular injury." It should be clarified that Gore Viabahn Stent Graft is for emergency treatment. Only limited information is available regarding the efficacy of Gore Viabahn Stent Graft. Whether a patient should be treated with Gore Viabahn Stent Graft must be determined taking into consideration the availability of other hemostatic measures. Based on the comments from the Expert Discussion, these precautions must be included in the instructions for use. Information regarding the hemostasis success rate and the incidence of endoleak should be collected through a use-results survey to take appropriate measures.

The safety evaluation of Gore Viabahn Stent Graft revealed many occlusion-related adverse events; 2 events of graft occlusion, 2 events of stenosis, 2 events of thromboembolism, and 2 events of collateral occlusion. However, Gore Viabahn Stent Graft was not associated with re-hemorrhage or death. Taking into consideration the comments from the Expert Discussion, these adverse events are clinically acceptable because the main trunk is closed to achieve hemostasis in vascular injury treatment. Although Gore Viabahn Stent Graft is expected to regain blood flow, only limited safety data are currently available. Given these points, relevant information should be collected through a use-results survey to take appropriate risk mitigation measures. The long-term safety of Gore Viabahn Stent Graft for more than 1 year was reported only in 5 publications. There is no sufficient data on its long-term safety. The instructions for use should include the precaution that "the long-term safety has not been fully established and sufficient observations are required after temporary hemostasis is achieved with Gore Viabahn Stent Graft." The applicant agreed. Gore Viabahn Stent Graft is intended to be used for primary hemostasis. In some cases, however, Gore Viabahn Stent Graft alone may provide long-term hemostasis

without additional treatment. Nevertheless, since no sufficient long-term data are available as mentioned above, information regarding the long-term results with Gore Viabahn Stent Graft, including secondary treatment, stent patency, and clinical outcome, should be collected through a use-results survey and provided to healthcare professionals. Other appropriate measures should also be taken.

6.(1).B.3) Appropriateness of use of literature data regarding Hemobahn in evaluation of Gore Viabahn Stent Graft

Of the publications found, Gore Viabahn Stent Graft was used in 15 publications and Hemobahn was used in 7 publications. Both devices were used in 1 publication and device information was not included in 1 publication. The differences between Gore Viabahn Stent Graft and Hemobahn are described in "1, History of Development, Use in Foreign Countries, and Other Information."

The applicant's explanation about the following advantages of Gore Viabahn Stent Graft over Hemobahn:
Gore Viabahn Stent Graft is less invasive because of its smaller diameters; it has a delivery system compatible with 0.035 and 0.014/0.018 inch guidewires, which are generally used in endovascular treatment; and it is expected to be associated with a lower incidence of endoleak than Hemobahn because of a change in the expansion mechanism for device deployment from "[redacted]" to "[redacted]," which enables [redacted] deployment of the device, resulting in a higher adhesiveness between the device and the lumen. The heparin-bonding layer of Stent Graft is intended to add resistance to thrombosis to the device surface. Considering that Gore Viabahn Stent Graft provides hemostasis by mechanical bonding between the affected artery and the device, the presence of the heparin-bonding layer will not affect the hemostatic performance of the device. The modifications from Hemobahn to Gore Viabahn Stent Graft are intended to improve the usability and increase the adhesiveness to blood vessels. It is, therefore, appropriate to include the literature data on Hemobahn in evaluation of Gore Viabahn Stent Graft.

PMDA's view:
Hemostatic procedures using covered stents or stent grafts have been established to a certain extent worldwide, and the purpose of the clinical evaluation of Gore Viabahn Stent Graft in the treatment of vascular injuries is to verify that Gore Viabahn Stent Graft can be accurately delivered to the target site and has a good hemostatic performance. The conditions of traumatic or iatrogenic vascular injuries, such as site and severity, vary among cases. It is necessary to collect available literature data as much as possible although such data may be limited. Given these points, it was reasonable to add the literature data on the previous generation product of Gore Viabahn Stent Graft to its clinical evaluation provided that their differences were clarified.

6.(1).B.4) Appropriateness of application sites of Gore Viabahn Stent Graft

The relevant academic societies requested the Needs Study Group to discuss the application of Gore Viabahn Stent Graft in the treatment of vascular injuries to the iliac and femoropopliteal arteries. On the other hand, in the Needs Study Group meeting, there were reportedly many opinions asking to collect as much information as possible so that Gore Viabahn Stent Graft could be used not only in the iliac and femoropopliteal arteries but also other clinically appropriate diseases and sites. The following comments were raised in the Expert Discussion: (1) Gore Viabahn Stent Graft would provide clinically significant benefits in the treatment of vascular injuries involving arteries, such as the main superior mesenteric artery, where vascular occlusion may cause severe harm to patients but the injuries may result in death if left untreated, and (2) Gore Viabahn Stent Graft will be more clinically useful when target blood vessels are not specified in detail provided that clearly high-risk sites are excluded from the indications.

In view of the comments from the Expert Discussion, PMDA's view on the application sites of Gore Viabahn Stent Graft:

- Multiple publications reported its successful placement and hemostatic performance, and it is reasonable to include the subclavian and iliac arteries in the application sites of Gore Viabahn Stent Graft.
- Currently, there are few reports or publications on the outcome of conventional treatments of traumatic or iatrogenic vascular injuries to the abdominal aortic branches (celiac, superior mesenteric, and renal arteries, and their branches). Considering the principle, nonclinical results, and hemostatic effect at other sites of Gore Viabahn Stent Graft, as well as the fact that coils, etc. are already used in the current treatment of abdominal aortic branches, the procedure lacks a novelty factor. Intra-abdominal hemorrhage is often difficult to manage. Gore Viabahn Stent Graft, as a life-saving device, has clinically significant benefits. On the basis of the comments from the Expert Discussion, it is possible to include the abdominal aortic branches in the application sites of Gore Viabahn Stent Graft. Further information regarding its use in these sites must be collected through a use-results survey to take appropriate risk mitigation measures as necessary.
- Both the carotid artery and the vertebral artery should be excluded from the application sites as with the coronary artery because of the high risk of occlusion.

The above arteries should be designated as the application sites of Gore Viabahn Stent Graft. The instructions for use must clarify that Gore Viabahn Stent Graft is intended to be used for life-saving emergency treatment. The intended use should be "Gore Viabahn Stent Graft is indicated for emergency treatment of patients who have blood leakage that is difficult to manage due to a traumatic or iatrogenic injury to the thoracic, abdominal, or pelvic artery with a reference vessel diameter of 4.0 to 12.0 mm, excluding injuries to the aorta, coronary artery, brachiocephalic artery, carotid artery, vertebral artery, and pulmonary artery."

6.(1).B.5) Post-marketing safety measures

PMDA's view:

To minimize the risk of vascular injury treatment with Gore Viabahn Stent Graft, physicians with sufficient knowledge about the anatomical requirements of vascular injury sites should select appropriate treatment methods and devices including conventional therapies, and physicians with sufficient experience in addressing problems, such as unsuccessful hemostasis and complications, should use Gore Viabahn Stent Graft. PMDA asked the applicant's opinions on these.

The applicant's response:

The applicant plans to include appropriate precautions in the instructions for use and to take measures to ensure the compliance with the guideline for proper use that would be prepared by a council on vascular injury treatment organized by the Japanese Society of Interventional Radiology (Japan IVR), which recommended the Needs Study Group to discuss Gore Viabahn Stent Graft.

PMDA's view:

PMDA generally agreed with the applicant's opinions and considered it necessary to add approval conditions 1 and 2 regarding the requirements for physicians and facilities, thorough training, and compliance to the guideline for proper use to ensure the full performance and safer use of Gore Viabahn Stent Graft. Since the clinical efficacy and safety data of Gore Viabahn Stent Graft are limited, PMDA instructed the applicant to collect relevant information through a use-results survey to take appropriate measures. A summary of the use-results survey is provided in Section 7.

The applicant's explanation:
The applicant plans to include a precaution in the instructions for use to enable treating physicians to decide the duration of antiplatelet therapy as needed because no recommendable guideline is available for antiplatelet therapy during vascular injury treatment and drug therapy for vascular injury treatment largely depends on comorbidities.

Taken together with the comments from the Expert Discussion, PMDA concluded that it would be reasonable to include the above precautions in the instructions for use as explained by the applicant and to collect information regarding antiplatelet therapy in the use-results survey.

6.(2) Vascular patency treatment (Attached document 6-2)

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

The applicant submitted clinical data from the Japanese clinical study (this study) of Gore Viabahn Stent Graft used to improve blood flow in patients with symptomatic PAD. This study was conducted in patients with a stenotic or occlusive symptomatic lesion(s) (length ≥10 cm, Rutherford category 2-5 [Table 12]) in the range from ≥1 cm distal to the SFA origin to ≥1 cm proximal to the medial epicondyle of the femur to evaluate the efficacy and invasiveness of Gore Viabahn Stent Graft in comparison with surgical bypass in a multicenter, prospective, non-randomized, single-arm design at 15 study sites in Japan (study period, April 2012 to August 2018). The primary efficacy endpoint was the "assisted-primary patency rate at Month 12[a]." The performance goal was 65% based on publications regarding surgical bypass. The primary safety endpoint was "invasiveness (number of postoperative hospital days and avoidance rate of general anesthesia). The safety results of Gore Viabahn Stent Graft were compared with the results of separate retrospective research on surgical bypass.[b]

Table 12. Rutherford category

Grade	Category	Clinical findings
0	0	Asymptomatic
I	1	Mild claudication
	2	Moderate claudication
	3	Severe claudication
II	4	Ischemic rest pain
III	5	Minor tissue loss
IV	6	Major tissue loss

Patients aged ≥20 years who met the following inclusion criteria were included in the study.

1) Patients have an occlusive lesion(s) of Rutherford category 2 to 5,
2) have an Ankle Brachial pressure Index (ABI) of the test limb of ≤0.9 or Toe Brachial pressure Index (TBI) of ≤0.5 within 30 days prior to the study treatment,
3) are candidates for surgical bypass, and
4) meet the following angiographic requirements as confirmed by perioperative assessment;
   (a) there is 1 or multiple new stenotic, occlusive, or stenotic and occlusive lesion(s), or re-stenosis, re-occlusion, or re-stenosis and re-occlusion after angioplasty, ≥10 cm in length with a stenosis

[a] The assisted-primary patency was defined as "no necessity of target lesion revascularization (TLR) procedure to restore the blood flow after occlusion and the presence of the blood flow at the treated site with the stent graft patent."

[b] This research was conducted from [redacted] to [redacted] at 6 study sites of this study where surgical bypass was performed at their departments. The inclusion and exclusion criteria that might affect the invasiveness of the treatment (e.g., Rutherford category, specification limits of ABI/TBI, and prior therapy) in this research were the same as those of this study. In the research, bypass surgeries conducted after January 1, [redacted] were included. [redacted]. The overall target sample size was 50. The primary research variables were (a) the number of postoperative hospital days, (b) the avoidance rate of general anesthesia during surgery, and (c) the avoidance rate of transfusion during surgery. The research included 68 patients. The Rutherford category was 2 in 10.3% of the research population, 3 in 64.7%, 4 in 10.3%, and 5 in 14.7%. The median number of postoperative hospital days was 12.5 days, with a mean of 16.2 days. The avoidance rate of general anesthesia during surgery was 25.0% (17 of 68 patients). The avoidance rate of transfusion during surgery was 94.1% (64 of 68 patients).

rate of ≥50% in the range from ≥1 cm distal to the SFA origin to ≥1 cm proximal to the medial epicondyle of the femur,

(b) the femoropopliteal artery proximal to the treated site, including the SFA origin, is not stenosed and is patent,

(c) the femoropopliteal artery distal to the treated site is patent (stenosis rate <50%),

(d) a ≥1 cm healthy blood vessel, 4.0 to 7.5 mm in diameter proximal and distal to the target lesion remains intact according to the operating instructions of the study device,

(e) at least 1 of the anterior tibial artery, posterior tibial artery, and peroneal artery is patent from the origin to the foot requiring no planned treatment within 12 months after the treatment with Gore Viabahn Stent Graft as confirmed by angiography (stenosis rate <50%), excluding the cases where there is a satisfactory patency with prior treatment,

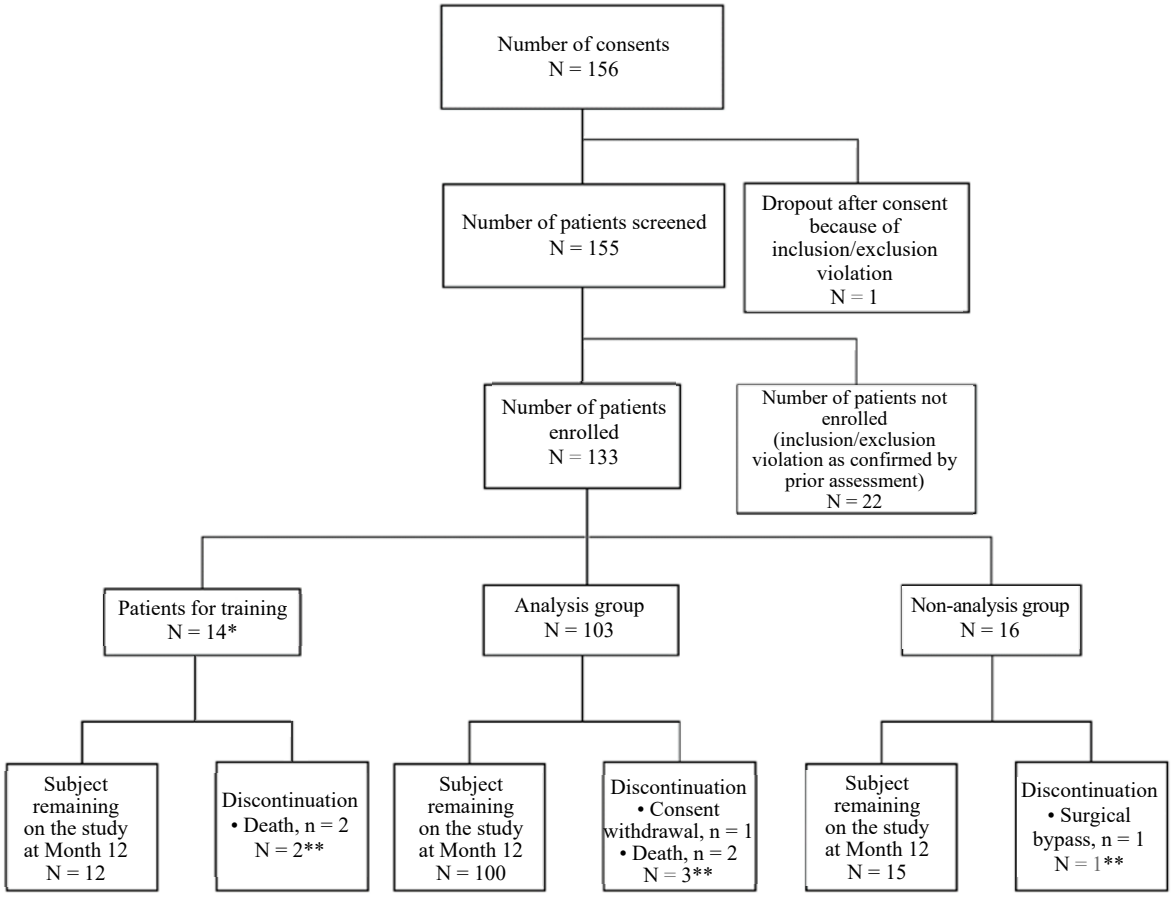
(f) a guidewire can pass through the target lesion and can be seen in the vascular true lumen distal to the target lesion, and

(g) the target lesion is pre-dilated without causing a waist in the PTA balloon before stent placement according to the operating instructions of the study device.

The primary exclusion criteria are shown below:

1) Patients have an aortoiliac artery disease with constriction of blood flow requiring treatment,
2) are classified into Rutherford category 5 with a sign of active infection,
3) have a lesion(s) of Rutherford category 6 in the test or non-test limb, or have a primary tissue loss affecting the area proximal to the proximal phalanx, or
4) have a lesion(s) of Rutherford category 5 in the non-test limb.

Of patients who provided consent to participate in the study, 133 patients were enrolled in the study and received the treatment with Gore Viabahn Stent Graft (Figure 7). Each study site was allowed to perform the test procedure in up to 2 patients for the training purpose. A total of 14 patients for training received the study treatment. A total of 119 patients, excluding the patients for training, were enrolled in the study. The eligibility of each subject was assessed by the case review committee. As a result, 16 patients were excluded from analyses because of, e.g., the violation of Inclusion criterion 4) as confirmed on angiograms, etc. immediately before and after the first stent placement. A total of 103 subjects were included in analyses.



* Adverse events reported in the patients for training are additionally listed on the list of adverse event in the clinical study report, but were not included in the analysis of any endpoint.
** Number of discontinuations at Month 12 follow-up

Figure 7. Flow chart of the clinical study

Table 13 shows the patient characteristics in the clinical study.

Table 13. Patient characteristics and pathological characteristics

		Analysis group	Training group	Non-analysis group
Number of subjects		103	14	16
Mean age (SD) (years)		74.2 (7.0)	72.9 (8.1)	72.6 (8.7)
Male (n)		85 (82.5%)	13 (92.9%)	12 (75.0%)
Smoking history	(Current smoker)	29 (28.2%)	5 (35.7%)	4 (25.0%)
	(Current non-smoker)	74 (71.8%)	9 (64.3%)	12 (75.0%)
Diabetes mellitus		62 (60.2%)	6 (42.9%)	9 (56.3%)
Hypertension		91 (88.3%)	13 (92.9%)	13 (81.3%)
Coronary artery disease		42 (40.8%)	6 (42.9%)	11 (68.8%)
Myocardial infarction		12 (11.7%)	0	4 (25.0%)
Prior treatment with PAD		89 (86.4%)	12 (85.7%)	15 (93.8%)
Drug therapy		87 (97.8%)	12 (100.0%)	15* (100.0%)
Kinesitherapy		7 (7.9%)	3 (25.0%)	0
Percutaneous intervention		27 (30.3%)	6 (50.0%)	9 (60.0%)
Surgical operation		5 (5.6%)	2 (16.7%)	2 (13.3%)
Baseline Rutherford category				
Category 2		45 (43.7%)	6 (42.9%)	6 (37.5%)
Category 3		55 (53.4%)	7 (50.0%)	9 (56.3%)
Category 4		1 (1.0%)	1 (7.1%)	0
Category 5		2 (1.9%)	0	1 (6.3%)
Ulcer in the test limb		2 (1.9%)	0	1 (6.3%)
Gangrene in the test limb		0	0	0
Target lesion length (cm)				
Mean (SD)		21.8 (5.8)	22.4 (2.3)	24.0 (6.5)
Median		22.0	23.0	24.0
Min - Max		10.0-37.0	17.0-25.0	11.0-32.3
Length (cm) of Gore Viabahn Stent Graft placed				
Mean (SD)		25.3 (6.3)	26.1 (3.3)	27.3 (6.7)
Median		25.0	26.5	29.0
Min - Max		12.0-38.0	19.0-30.0	15.0-38.0
Severity of calcification	None	28 (27.2%)	5 (35.7%)	5 (31.3%)
	Mild	52 (50.5%)	6 (42.9%)	6 (37.5%)
	Moderate	22 (21.4%)	1 (7.1%)	4 (25.0%)
	Severe	1 (1.0%)	2 (14.3%)	1 (6.3%)

* Fifteen subjects were eligible for drug therapy.

6.(2).A.1) Primary endpoint

Of 103 subjects in the analysis group, 100 subjects with eligible patency data at Month 12 were included in the primary efficacy evaluation. The following 3 subjects in the analysis group were ineligible: 1 subject who died from respiratory failure associated with interstitial pneumonia on Day 92; 1 subject who died from cerebral infarction on Day 240; and 1 subject who missed scheduled visits after the Month 6 visit. The analysis showed the assisted-primary patency rate of 91.0% (91 of 100 subjects, lower limit of the 95% confidence interval 86.3%), meeting the performance goal of 65%. As shown in Table 14 and Figure 8, the Kaplan-Meier estimate of assisted-primary patency rate was 94.1% up to Day 365 and 83.3% up to Day 760.[c]

The primary safety evaluation demonstrated that the median number of postoperative hospital days in 103 subjects in the analysis group was 2.0 days with a mean of 3.5 days, showing that the placement of Gore Viabahn Stent Graft was associated with a shorter hospital stay than that of surgical bypass (median 12.5 days, mean 16.2 days). No subject in the analysis group required general anesthesia (avoidance rate of general anesthesia 100%), indicating that the treatment with Gore Viabahn Stent Graft is more likely to avoid general anesthesia compared with surgical bypass (avoidance rate of general anesthesia 25%).

[c] Corrected after the meeting of the Committee on Medical Devices and *In-vitro* Diagnostics: before correction "the Kaplan-Meier estimate of assisted-primary patency rate was 94.1% on Day 365 (Table 14, Figure 8)"

Table 14. Kaplan-Meier estimate of assisted-primary patency rate (as of [redacted])

Number of postoperative days	Number of subjects at start of each interval	Number of events per interval*	Number of subjects censored per interval*	Patency (%)	95% CI
0	103	0 (0)	0 (0)	100.0%	(100.0%, 100.0%)
1-37	103	1 (1)	1 (1)	99.0%	(93.2%, 99.9%)
38-121	101	2 (3)	0 (1)	97.1%	(91.2%, 99.0%)
122-212	99	3 (6)	2 (3)	94.1%	(87.3%, 97.3%)
213-365	94	0 (6)	15 (18)	94.1%	(87.3%, 97.3%)
366-395	79	3 (9)	10 (28)	90.3%	(82.0%, 94.8%)
396-760	66	4 (13)	60 (88)	83.3%	(72.3%, 90.3%)

* The figures in parentheses represent the cumulative number of events and that of subjects censored up to each interval.

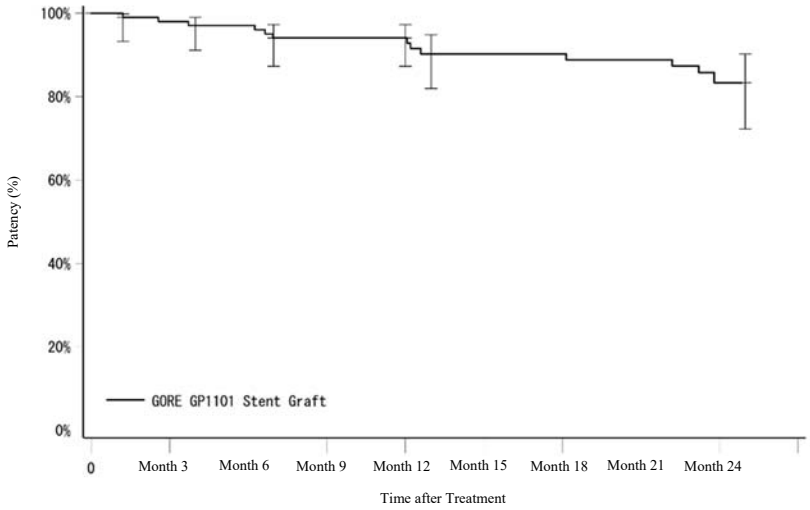


Figure 8. Kaplan-Meier estimate of assisted-primary patency rate

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

The technical success rate (defined as the residual stenosis rate of <30% as confirmed by postoperative angiography after the completion of placement of Gore Viabahn Stent Graft) was 99.0% (102 of 103 subjects). The treatment with Gore Viabahn Stent Graft technically failed only in 1 subject with a residual stenosis rate of 30% after the treatment. The Kaplan-Meier estimate of the primary patency (defined as no TLR due to re-stenosis or occlusion at the treated site and no occlusion at the treated site) rate was 92.1% on Day 365, while that of the secondary patency (defined as no surgical bypass and no occlusion at the treated site) rate was 98.0% on Day 365. The Kaplan- Meier estimate of TLR avoidance rate was 93.1% on Day 365. A total of 12 subjects required TLR[d] more than once by Day 395. The first TLR was performed in 1 subject between Days 38 and 121, 4 subjects between Days 122 and 212, 2 subjects between Days 213 and 365, and 5 subjects between Days 366 and 395. The limb salvage rate (defined as no major amputation of the test lower limb after treatment) was 100% in this study. The clinical success (defined as ≥1 improvement in Rutherford category after treatment lasting up to the end

[d] TLR was to be performed based on the final assessment by the investigator or subinvestigator with reference to the following conditions.
- In the cases of i) to iv), the necessity of further assessment must be discussed.
  i) Aggravation by ≥0.15 in ABI of the test limb
  ii) ≥1 aggravation in Rutherford category in the test limb
  iii) Peak systolic velocity ratio (PSVR) >2.5 in the target lesion as measured by duplex ultrasound (DUS)
  iv) Acute aggravation in symptoms in the test limb (e.g., blue toe syndrome)
- In the case of ≥50% stenosis as confirmed by angiography, TLR should be considered.

of each interval) rate at Month 12 was 90.9% (90 of 99 subjects). Of the 9 subjects with clinical failure, 8 subjects had the same Rutherford category. The category worsened in 1 subject compared with baseline.

6.(2).A.3) Adverse event

No thrombosis, stent fracture, or major lower limb amputation of the test limb was reported up to Month 12. Death occurred in 2 subjects (1 subject from respiratory failure associated with interstitial pneumonia on Day 92; and the other subject from cerebral infarction on Day 240).

A total of 354 adverse events were reported in the analysis data set. Investigational device- or procedure-related serious adverse events and serious adverse events of unknown cause were reported in 9 subjects (8.7%, 14 events in total) (Table 15). These serious adverse events were 1 event of renal failure chronic aggravated, 1 event of haematoma, 11 events of stent-graft stenosis or occlusion, and 1 event of infection. All events resolved after treatment. Of these, events related to the investigational device were 8 events of stent-graft occlusion in 4 subjects, and 3 events of stent-graft re-stenosis in 2 subjects. Of these, 7 events required thrombectomy or thrombolysis and 4 events required additional stent treatment.

Table 15. Investigational device- or procedure-related serious adverse events

Subject	Test limb	Number of days to onset	Details of adverse event	Causality	Treatment
1	Right	4	Renal failure chronic aggravated	Procedure-related	Blood purification therapy
2	Left	0	Hematoma in the toes, above the knee, sural region	Procedure-related	Elastic bandage, antiphlogistic analgesic
3	Right	361	• Intrastent-graft occlusion in the right SFA • Thrombectomy in the PTA through the right common femoral artery access • Placement of additional set of Gore Viabahn Stent Graft (5 mm × 5 cm)	Investigational device-related	POBA, mechanical thrombectomy, placement of additional device
4	Right	547	Intrastent-graft thrombotic occlusion in the right SFA	Investigational device-related	POBA, thrombolysis
5	Left	207	Occlusion at the proximal end of the stent-graft in the left SFA	Investigational device-related	Heparin, POBA, thrombolysis
	Left	320	Intrastent-graft occlusion in the left SFA	Investigational device-related	Thrombus suction, placement of additional set of Gore Viabahn Stent Graft, heparin
	Left	393	Intrastent-graft re-occlusion in the left SFA	Investigational device-related	POBA, thrombolysis, mechanical thrombectomy, anticoagulant
	Left	489	Intrastent-graft re-occlusion in the left SFA	Investigational device-related	POBA, thrombolysis, mechanical thrombectomy
6	Left	367	Intrastent-graft re-stenosis in the left SFA	Investigational device-related	POBA
	Left	609	Stenosis at the distal end of the stent-graft in the left SFA	Investigational device-related	POBA
7	Right	365	Stenosis at the distal end of the stent-graft in the right SFA	Investigational device-related	POBA
8	Right	1	Infection, possibly associated with catheterization	Procedure-related	Antiphlogistic analgesic, antibiotic
9	Right	202	Intrastent-graft occlusion in the right SFA	Investigational device-related	POBA, placement of additional device
	Right	265	Intrastent-graft occlusion in the right SFA	Investigational device-related	POBA, placement of additional device, thrombus suction

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

PMDA reviewed the intended use of Gore Viabahn Stent Graft mainly focusing on the following points.

6.(2).B.1) Clinical positioning of Gore Viabahn Stent Graft

Gore Viabahn Stent Graft was developed as a safe and effective endovascular treatment device to treat TASC II Type C or D lesions, whose currently recommended first-line treatment is surgical bypass. The performance goal in this study was chosen with reference to the results of surgical bypass. On the other hand, candidates for surgical bypass in clinical practice are severer patients (e.g., Rutherford category ≥4) and patients with complicated lesions (e.g., severely calcified lesion). PMDA asked the applicant to clarify whether the results of this study that included only 3 subjects with Rutherford category ≥4 and 1 subject with a severely calcified lesion were sufficient to designate Gore Viabahn Stent Graft as an alternative option to surgical bypass.

The applicant's response:

A majority of subjects enrolled in this study were patients with a TASC II Type C (n = 74) or D (n = 10) lesion. The TASC II recommends surgical bypass to these patients. The clinical study showed the assisted-primary patency rate of 91.0% with Gore Viabahn Stent Graft at Month 12. This result significantly exceeded the performance goal (PG) of 65%, which was determined with reference to literature data on surgical bypass, suggesting the effectiveness of Gore Viabahn Stent Graft even in patients with a TASC II Type C or D lesion (Table 16).

Table 16. Assisted-primary patency at Month 12 by TASC II classification

		Assisted-primary patency rate at Month 12
TASC II classification	Number of eligible subjects	Patent
Overall	100	91 (91.0%)
Type B lesions	16	16 (100.0%)
Type C lesions	74	65 (87.8%)
Type D lesions	10	10 (100.0%)

The TASC II recommends an appropriate treatment method be selected based on lesion morphology but not patient's clinical symptoms, such as Rutherford category. This guideline identifies clinical variables, including the severity of ischemia, as well as diabetes, renal failure, and smoking as factors that might affect treatment outcome. According to the guideline, the number of runoff blood vessels[e] can also affect treatment outcome. The guideline mentions the frequent occurrence of multiple lesions in blood vessels below the popliteal artery in patients with critical limb ischemia. Gore Viabahn Stent Graft should be used with care in the treatment of a stenotic or occlusive lesion in patients without a peripheral runoff blood vessel that is patent up to the ankle. This precaution is included in the instructions for use of Gore Viabahn Stent Graft.

The possible reason for the limited number of subjects with Rutherford category 4 or 5 enrolled in the study is the presence of clinical symptoms associated with these lesions in the popliteal artery. However, a lesion in the popliteal artery itself is a key factor of device malfunctions. For this reason, the use of Gore Viabahn Stent Graft should not be decided based on clinical symptoms, such as Rutherford category, and should be cautioned in patients without a runoff blood vessel.

PMDA's view:

The TASC II, the medical practice guideline for PAD issued in 2007 by 16 academic societies in the US, Europe and Asian countries, classifies arteriosclerotic lesions in the femoropopliteal artery into Types A to D according to their description. The first-line treatment recommended in the guideline is endovascular treatment for Type A or B lesions, and surgical bypass for Type C or D lesions. In Japan,

[e] Runoff blood vessels represent blood vessels flowing out from the SFA.

the approved stents for SFA are used for lesions ≤15 cm in length, which is one of the definitions of Type B. In the US, on the other hand, the use of SFA stents is not necessarily limited to ≤15 cm lesions.

Currently, many endovascular treatment devices are available, with the improved outcome. Depending on the conditions of lesion or patient, Type C or D lesions are also treated by endovascular treatment, which is less invasive than the conventional surgical treatment. The European guideline recommends endovascular treatment as the first-line treatment of Type C lesions with Level of Evidence C (Class I).[21] The Society for Vascular Surgery also issued a guideline in 2015. According to the guideline, invasive treatments, including endovascular treatment and surgical treatment, should be limited to severe patients who do not improve with conservative treatment. The guideline reports that endovascular treatment is associated with a lower 30-day postprocedural incidence of complications in the lower limbs than surgery, while surgery is superior to endovascular treatment in the primary patency rate because of a higher incidence of technical failure with endovascular treatment.[22]

Gore Viabahn Stent Graft is available in various sizes up to 25 cm for the treatment of lesions in the SFA. It can be used to treat ≥15 cm lesions classified into Type C or D, longer than ≤15 cm lesions that are conventionally treated with approved SFA stents. Since the efficacy of endovascular treatment of Type C or D lesions has not been fully established, the efficacy and safety of Gore Viabahn Stent Graft should be thoroughly evaluated based on the results of this study. If this study shows good results of Gore Viabahn Stent Graft in the treatment of ≥15 cm lesions, it is of clinical significance to make Gore Viabahn Stent Graft available to healthcare professionals as a treatment option.

6.(2).B.2) Efficacy of Gore Viabahn Stent Graft

PMDA asked the applicant to explain the appropriateness of PG and the efficacy of Gore Viabahn Stent Graft in this study.

The applicant's explanation:

(a) Rationale

To determine PG for the clinical study, literature search was conducted on the results of the primary patency rate of surgical bypass, the standard treatment of long-segment lesions in Japan. The literature search included publications from not only prospective studies but also retrospective studies in and outside Japan, and 18 publications were identified. These publications showed similar results of the primary patency rate at Year 1 between Japanese patients and non-Japanese patients, indicating that the effects of regional differences, including those in ethnicity and lifestyle habits, on the patency rate do not need to be considered. The procedures, graft materials, concomitant devices, and concomitant medications were also shown to be similar in and outside Japan. Of the 18 publications obtained, 1 Japanese publication[23] and 4 foreign publications[24-252627] used the same definition of primary patency rate as this study (no requirement for additional treatment and no occlusion). In these publications, the weighted mean of the primary patency rate was 79.6%.

On the basis of this primary patency rate (79.6%) and taking into consideration differences in follow-up details, publication bias, and differences in analysis methods, the primary patency rate with surgical bypass in clinical practice was estimated to be approximately [redacted]%. Considering its planned sample size, PG of 65%, and power, the design of this study makes study success difficult to achieve unless the assisted-primary patency rate was actually ≥[redacted]%. If this study demonstrates the PG of >65% with Gore Viabahn Stent Graft, it can be considered that the efficacy of Gore Viabahn Stent Graft is comparable to that of surgical bypass, which is estimated to provide the assisted-primary patency rate of approximately [redacted]%.

(b) Differences in patient characteristics between publications used to select the PG and this study

Subjects who received Gore Viabahn Stent Graft tended to be older. Sex and other medical history of subjects in this study were almost similar to those in the 5 publications used to select the PG when such comparisons were possible. The Rutherford category was not necessarily clear in all of the publications. The category determined based on reported symptoms (e.g., claudication and severe ischemia) varied among the publications. This means that the outcome reported in the publications used to select the PG reflects the general outcome of the surgery. The number of subjects with lesions classified into Rutherford category 4 or 5 enrolled in the clinical study of Gore Viabahn Stent Graft was low, likely because of the specification on the number of runoff blood vessels as explained in Section 6.(2).B.1).

On the basis of the above, the efficacy of Gore Viabahn Stent Graft is discussed as shown below.

Gore Viabahn Stent Graft is an alternative option to surgical bypass in the treatment of complicated TASC II Type C or D lesions having runoff blood vessels. Gore Viabahn Stent Graft is widely used overseas, with accumulating clinical results of Gore Viabahn Stent Graft in the treatment of long-segment lesions (Table 17).

Table 17. Results of foreign clinical studies of Gore Viabahn Stent Graft in long-segment lesions

		Lammer[28,29] N = 72	Saxon[30] N = 113 (119 limbs)	Zeller[31] N = 71
Study design		Multicenter, prospective, randomized, single-blind	Multicenter, prospective, single-arm	Multicenter, prospective, single-arm
Device model		Gore Viabahn Stent Graft	Gore Viabahn Stent Graft	Gore Viabahn Stent Graft
TASC II	A	0	17 (14%)	0
	B	20 (28%)	30 (25%)	0
	C	18 (25%)	35 (29%)	71 (100%)
	D	34 (47%)	37 (31%)	
Mean lesion length		19.0 ± 6.3 cm	19 cm (5-37 cm)	26.5 ± 5.31 cm (20-40 cm)
Percentage of occlusion		56 (79%)	67 (56%) (mean length of occlusion, 22 cm)	65/70 (92.9%)
Primary patency rate*	Year 1	70.9% (ITT) 78.1% (TPP)	73%	67.0%
	Year 2	63.1%(ITT) 69.4% (TPP)	—	—
Secondary patency rate	Year 1	89.9% (TPP)	92%	96.9%
	Year 2	89.0%	—	—
TLR avoidance rate		84.6% (Year 1) 79.4% (Year 2)	—	78.2% (Year 1)

* The primary patency rate was defined as follows:
Lammer: PSVR of ≤2.5 as measured by DUS, re-stenosis rate of ≤50%, and no TLR required at the treated site
Saxon: No re-intervention required at the treated site, PSVR of <2.5 as measured by DUS, no findings of re-stenosis or occlusion, or no findings showing stenosis rate of >50% as confirmed by angiography
Zeller: No findings of re-stenosis or occlusion at the treated site

The primary patency rate of the long-segment lesions with Gore Viabahn Stent Graft in the foreign clinical studies was approximately 70% at Year 1, with a TLR avoidance rate of approximately 80%. Although the results somewhat varied among the studies, these studies demonstrated the consistent results of Gore Viabahn Stent Graft irrespective of lesion length.

Although their target lesion lengths are different from those of Gore Viabahn Stent Graft, “Zilver PTX Drug-eluting Peripheral Stent” (Approval number 22400BZX00013000), “Misago” (Approval number 22400BZX00463000), “SMART Stent” (Approval number 22500BZX00195000), and “SMART CONTORL Stent” (Approval number 22500BZX00194000) are approved as SFA stents in Japan. Table 18 shows a comparison of the TLR rate between these stents and Gore Viabahn Stent Graft. A

comparison of the TLR rate is difficult because the definition of the TLR rate varied among the studies. For this reason, the TLR rate at Month 12 was compared between the stents.

Table 18. Comparison of clinical study results of approved products at Year 1

	Gore Viabahn Stent Graft	Zilver PTX (multicenter, global study)	Misago (OSPREY Japanese study)	Misago (OSPREY LONG Study)	SMART** (Study SM-01)
Mean lesion length	218 ± 58 mm (N = 103)	54.6 ± 40.7 mm (N = 242)	79.113 ± 37.947 mm (N = 50)	139.410 ± 42.209 mm (N = 34)	92.1 ± 38.3 mm (N = 51)
TLR rate*	12% (12/100)	9.5% (21/220)	18.0% (9/50)	20.6% (7/34)	7.8% (4/51)
Mortality	1.9% (2/103)	3.4% (8/235)	2.0% (1/50)	2.9% (1/34)	0.0% (0/51)
Incidence of lower limb amputation	0.0% (0/103)	0.5% (1/220)	0.0% (0/50)	0.0% (0/34)	0.0% (0/51)
Incidence of thrombosis	Thrombosis 0.0% (0/103)	Thrombosis at the target lesion 2.6% (6/235)	Stent thrombosis 0.0% (0/50)	Stent thrombosis 0.0% (0/34)	No data

* Clinically drive TLR for Zilver PTX, and all kinds of TLR for Gore Viabahn Stent Graft, Misago, and SMART stent
** Data at Year 1

The mean lesion length in this study was longer than that in the other clinical studies. Nevertheless, Gore Viabahn Stent Graft was associated with a similar TLR rate to that of the SFA stents approved for the treatment of lesions ≤15 cm, indicating the non-inferiority of Gore Viabahn Stent Graft to the approved products in terms of the outcome. Given this, the results of this study and the foreign clinical studies, etc. demonstrate the safety and efficacy of Gore Viabahn Stent Graft in patients with long-segment lesions, who are candidates for the treatment with Gore Viabahn Stent Graft.

PMDA's view:
Even when the bias, power, etc. as explained by the applicant were taken into consideration, the PG of this study was slightly lower than it should be, given the primary patency rate of approximately 80% in the reference publications on surgical bypass (the lower limit of 95% confidence interval, approximately 75%) and the fact that many lesions treated with Gore Viabahn Stent Graft were TASC II Type C lesions. In addition, the assisted-primary patency rate is naturally higher than the primary patency rate. There is a concern that this PG was too conservative. Nevertheless, this study showed a primary patency rate of 92.1% and a clinical success rate (defined as ≥1 improvement in Rutherford category at 12 months post-procedure) of 90.9% (90 of 99 patients). The treatment outcome was satisfactory even in TASC II Type C lesions and long-segment lesions (mean lesion length of 21.8 cm in this study). A simple comparison between Gore Viabahn Stent Graft and the approved SFA stents in Japan (Table 18) was difficult because the patient characteristics varied among the clinical studies. Nevertheless, the results of this study, which involved more complicated lesions, were not inferior to those of the approved stents.

The results of this study indicate the efficacy of Gore Viabahn Stent Graft, as an endovascular treatment device, in the treatment of longer-segment Type C or D lesions compared with those treated with the approved products, within the scope of length targeted in this study. Given the evidence in the guidelines, etc., however, there are not sufficient grounds for recommending endovascular treatment with Gore Viabahn Stent Graft as the first-line treatment of all TASC II Type C or D lesions, whose current first-line treatment is surgery. It is important to provide the above information in the instructions for use to ensure that physicians make the appropriate decision.

6.(2).B.3) Safety of Gore Viabahn Stent Graft

6.(2).B.3).(a) Adverse event

PMDA asked the applicant to explain the details of the 1 subject who experienced aggravation in Rutherford category from baseline and the incidence of stent-graft thrombosis.

The applicant's explanation:
The 1 subject who experienced aggravation in Rutherford category from baseline had stent graft occlusion as detected by Month 3 follow-up. The subject underwent TLR by mechanical thrombectomy, with the outcome of unrecovered. The subject withdrew the consent and was discontinued from this study on Day 306.

6.(2).B.3).(b) Antiplatelet therapy

In this study, dual antiplatelet therapy (DAPT) with ≥2 antiplatelet drugs i.e., aspirin and thienopyridine drugs as selected at the discretion of the investigator or subinvestigator was started ≥48 hours before the endovascular treatment. The DAPT was to be performed for the first ≥6 months postoperative and was recommended to be continued for 12 months postoperative.

PMDA asked the applicant to discuss appropriate antiplatelet therapy in the post-marketing setting based on the characteristics of Gore Viabahn Stent Graft.

The applicant's explanation:
The following antiplatelet drugs were administered in this study: Aspirin 96.1%, clopidogrel 75.7%, ticlopidine 16.5%, and cilostazol 32.0%. DAPT was given to 98.0% of the subjects at Month 6 follow-up and 86.3% at Month 12 follow-up.

Outside Japan, there is no standard recommended duration of DAPT for the treatment with Gore Viabahn Stent Graft. According to multiple publications,[28,30-32] patients treated with Gore Viabahn Stent Graft with the heparin-bonding layer had continued DAPT for ≥6 months. In designing this study, it was considered essential to continue DAPT for the first 6 months postoperative because Gore Viabahn Stent Graft requires longer period than BMSs for the endothelialization of the graft surface at the implantation site due to the structure of its stent graft being different from BMSs and consequently requiring DAPT for a longer period, as well as based on the foreign reports on the duration of DAPT. Ideally, DAPT should be continued for an extended period because the time required for endothelialization is unclear. However, long-term DAPT is difficult in some patients because of complications, etc. In addition, a publication has reported that DAPT for ≥6 months increases the risk of hemorrhagic events, although it is a report from patients with coronary artery disease. Together with the advice from the physicians of the case review committee, subjects were recommended to continue DAPT from Months 6 to 12.

6.(2).B.3).(c) Safety compared with approved endovascular treatment devices

As shown in Table 18, the safety of Gore Viabahn Stent Graft, despite its longer target lesions, was non-inferior to the approved SFA stents even in terms of the incidence of major adverse limb events (MALE).

PMDA's view on the safety of Gore Viabahn Stent Graft:
No subject reported thrombosis as an adverse event. However, 8 events of stent-graft occlusion and 3 events of re-stenosis were reported. Of these, 7 events required thrombectomy or thrombolysis. These events were occlusion or stenosis likely attributable to thrombosis. The definition of thrombosis could have been unclear in the protocol, and more thrombosis might have possibility occurred, other than the above cases. PMDA asked the applicant to explain the definition of stent-graft thrombosis in this study

and the safety of Gore Viabahn Stent Graft, considering some subjects might have experienced thrombosis in the clinical study.

The applicant's explanation:
Stent-graft thrombosis was not defined for this study because stent-graft thrombosis was not an event of special interest. Thrombosis was, therefore, diagnosed according to the conventional definition of stent thrombosis in the field of the endovascular treatment of the coronary artery and the general practice in the management of stent thrombosis in peripheral blood vessels of the limbs.

The reports from the study sites in the list of adverse events were reviewed according to the definition of stent-graft thrombosis as "an occlusive event that is attributable to a thrombus as clinically confirmed and is identified by diagnostic imaging." No study site reported stent-graft thrombosis. Accordingly, it was concluded that there was "no report." To confirm the occurrence of thrombosis, physician's clinical assessment is required. It is reasonable to determine that no thrombosis occurred based on the reports from the study sites. Occlusive events might have occurred through the following 2 possible mechanisms:

- Neointimal thickening promotes edge stenosis, which affects the blood flow in the stent graft, resulting in thrombotic stent-graft occlusion
- A thrombus attaches to the surface of the stent-graft lumen wall, which affects the blood flow in the stent graft, resulting in stent-graft occlusion.

In general, occlusion in the acute phase (approximately 30 days postoperative) is possibly associated with a thrombus. Occlusion, however, can result from various factors. Occlusion leads to thrombosis in the stent graft once occlusion occurs regardless of its cause. It is, therefore, challenging to identify the cause of each occlusion event. Since cases of thrombus-related occlusion cannot be fully ruled out, it is difficult to determine the incidence of stent-graft thrombosis.

The clinical risk of thrombosis can be assessed based on the presence of acute limb ischemia (ALI). ALI is defined as a sudden decrease in the blood flow that may result in lower limb amputation regardless of its cause. This condition requires immediate intervention once it occurs. As an event associated with the risk of lower limb amputation in the presence of vascular occlusion, the incidence of ALI is a very important index from the clinical viewpoint. In this study, neither ALI nor lower limb amputation was reported. A comparison between Gore Viabahn Stent Graft and BMSs overseas also showed no difference in the incidence of ALI. Gore Viabahn Stent Graft is not associated with a higher risk of ALI than the BMSs. Table 19 shows the comparison.

Table 19. Comparison of the incidence of ALI between Gore Viabahn Stent Graft and BMSs (Year 1 follow-up)[28]

	Gore Viabahn Stent Graft, n = 66	BMS* n = 63	*P*-value
Re-stenosis (>50%)	9 (14%)	22 (35%)	0.007
Occlusion	6 (9%)	4 (6%)	0.74
Acute lower limb ischemia	1 (1.5%)	0	1.0

* Life Stent, Protégé EverFlex Stent, and SMART-Control stent. These were selected because their primary patency rate at Year 1 was ≥80%.

These results show that Gore Viabahn Stent Graft is not associated with a particularly higher safety risk of thrombosis than the BMS.

PMDA's view on the safety of Gore Viabahn Stent Graft:
Gore Viabahn Stent Graft was used to treat longer lesions than those for the SFA stents in this study, without significant safety concerns. However, the definition of stent thrombosis in the SFA has not been established. It is difficult to confirm that each occlusive lesion was caused by a thrombus. In this study, 14 events of stent-graft occlusion were reported in 10 subjects. Six of these subjects required interruption of the antiplatelet therapy. In addition, literature data show 1 event of ALI (incidence, 1.5%). For these reasons, it cannot be concluded that Gore Viabahn Stent Graft is associated with a low risk of stent thrombosis. Unlike conventional SFA stents, Gore Viabahn Stent Graft has a covered stent structure and is used in longer lesions than those used with conventional stents. In addition, Gore Viabahn Stent Graft has the heparin-bonding layer. The recommended duration of DAPT must be clearly communicated to healthcare professionals. The risk of continuing DAPT for a certain period should also be warned appropriately. PMDA instructed the applicant to collect further information through a use-results survey on stent thrombosis and stent-graft occlusion, including suspected cases, to take appropriate risk mitigation measures.

The applicant agreed and included the following precautions in the instructions for use: "Prior to the endovascular treatment of stenotic or occlusive lesions, antiplatelet therapy should be started at the discretion of the physician. It is highly recommended that ≥2 antiplatelet drugs, including anticoagulants, be administered for the first ≥6 months postoperative. It is also recommended to continue the antiplatelet therapy from 6 months postoperative to 12 months postoperative."

6.(2).B.4) Justification for not determining upper limit for target lesion length of Gore Viabahn Stent Graft

The proposed target lesion length is ≥10 cm. No upper limit of target lesion length is determined. This study, in which lesions with a mean length of 21.8 cm (10.0-37.0 cm) were treated, demonstrated a comparable outcome to surgery or endovascular treatment of TASC II Type A or B lesions in the SFA, and no tendency for the outcome to be poor in proportion to the lesion length (Table 20). Besides, the length of the SFA where Gore Viabahn Stent Graft is planned to be used is generally approximately 30 cm in Japanese patients. Taken together with the comments from the Expert Discussion, PMDA concluded that the efficacy and safety of Gore Viabahn Stent Graft with no upper limit determined for target lesion length are assured in lesions that are expected to be treated with Gore Viabahn Stent Graft.

Table 20. Assisted-primary patency rate by target lesion length

		Assisted-primary patency at Month 12
	Number of subjects	Patent
Target lesion length	100	91 (91.0%)
10–15 cm	12	12 (100.0%)
15–20 cm	21	20 (95.2%)
20–25 cm	34	32 (94.1%)
25–30 cm	23	18 (78.3%)
30–35 cm	8	7 (87.5%)
35–40 cm	2	2 (100.0%)

On the other hand, as described above, Gore Viabahn Stent Graft is associated with the risk of stent thrombosis and therefore requires the prolonged use of DAPT compared with that with approved metal stents used to treat lesions in the SFA. This study included only 10 patients with TASC II Type D lesions. It is appropriate to make decisions on whether to use Gore Viabahn Stent Graft to treat long-segment lesions after fully assessing its risk-benefit balance based on lesion morphology and the risk of DAPT. This should be mentioned in the instructions for use. PMDA determined that the applicant should collect

sufficient information regarding the safety of Gore Viabahn Stent Graft in the treatment of longer-segment lesions through a use-results survey to take appropriate risk mitigation measures as necessary.

On the basis of the expert adviser's suggestion to change the target region to the "SFA" in order to clarify the exclusion of the popliteal artery, PMDA instructed the applicant to clearly describe this information in the intended use. The applicant agreed.

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

The applicant submitted a summary of the use-results survey of each of traumatic or iatrogenic vascular injury treatment and vascular patency treatment.

7.A.(1) Treatment of traumatic or iatrogenic vascular injury

The applicant's explanation:

In order to verify the efficacy and safety of Gore Viabahn Stent Graft in the treatment of patients with a traumatic or iatrogenic injury to the thoracic, abdominal, or pelvic artery, excluding injuries to the aorta, coronary artery, brachiocephalic artery, carotid artery, vertebral artery, and pulmonary artery, the applicant plans to conduct a use-results survey for [redacted] years from the approval date in 30 patients with a traumatic or iatrogenic injury to the thoracic, abdominal, or pelvic artery with a reference vessel diameter of 4.0 to 12.0 mm, excluding injuries to the aorta, coronary artery, brachiocephalic artery, carotid artery, vertebral artery, and pulmonary artery. Each patient will be followed up for 1 year after the treatment. The proposed key survey item is "successful implantation of Gore Viabahn Stent Graft or hemostasis." Patient characteristics, implantation or hemostasis success, and serious adverse events/malfunction at the time of treatment, as well as serious adverse events/malfunctions and interventions thereof at Year 1 will be investigated in the survey.

7.A.(2) Vascular patency treatment in SFA

The applicant's explanation:

In order to verify the efficacy and safety of Gore Viabahn Stent Graft in the treatment of patients with symptomatic PAD having a target lesion in the SFA in the post-marketing setting, the applicant plans to conduct a use-results survey in 250 patients with symptomatic PAD having a target lesion ≥10 cm in the SFA with a reference vessel diameter of 4.0 to 7.5 mm. Each patient will be followed up for 5 years after the treatment. The proposed key survey item is "stent fracture." Rutherford category, ABI (or TBI), duplex ultrasound, blood pressure, and plain X-ray (plain X-ray alone from Months 36 to 60, or plain X-ray assessment at Months 24 and 48 only when stent fracture is suspected), and adverse events will be investigated at the time of treatment, and Months 12, 24, 36, 48, and 60.

7.B Outline of the review conducted by PMDA

7.B.(1) Treatment of traumatic or iatrogenic vascular injury

PMDA's view:

Since no prospective clinical data are available at present, and a very limited number of cases have been reviewed in the publications, a use-results survey on the vascular injury treatment with Gore Viabahn Stent Graft should be conducted to collect relevant information in the clinical setting by eliminating biases as practically as possible. On the basis of such newly available information, appropriate measures must be taken. The safety of Gore Viabahn Stent Graft can be affected by not only its performance but also a surgeon's decision on use, procedure, etc. On the basis of the comments from the Expert Discussion, in addition to the above survey items, information regarding reasons for selecting the treatment with Gore Viabahn Stent Graft should be collected from consecutive patients as practically as

possible. The patency of the treated artery, patency of Gore Viabahn Stent Graft, adverse events (e.g., ischemic change in peripheral organs, re-hemorrhage, and endoleak), and additional treatments should be investigated at Months 1, 6, and 12 to evaluate middle- and long-term clinical results. In addition, the details of antiplatelet therapy used in each patient should be investigated to accumulate information on antiplatelet therapy in the clinical setting. On the basis of such information, appropriate risk mitigation measures should be taken as necessary. Given the above, PMDA asked the applicant to amend the draft plan of the use-results survey.

The applicant amended the draft plan accordingly and submitted a new draft plan of the use-results surveys for 5 years in total (sales preparation period [redacted] months, registration period [redacted] years, follow-up period 1 year, survey form collection/analysis/data lock period [redacted] months).

PMDA considered it necessary to add approval conditions 1 and 2 to ensure the full performance and safer use of Gore Viabahn Stent Graft because it must be used by physicians who have undergone full training on the pathology of each target disease, anatomical characteristics, device handling, etc. at medical institutions equipped with an emergency system so that serious adverse events caused by implantation of Gore Viabahn Stent Graft can be treated immediately and appropriately.

7.B.(2) Vascular patency treatment

PMDA asked the applicant to explain the rationale for the proposed sample size.

The applicant's explanation:

In general, BMS implantation in the SFA is associated with the risks of "stent fracture" and "stent thrombosis." At the start of this study, stent fracture was reported in <0.02% of patients treated with Gore Viabahn Stent Graft ([redacted] sets) in foreign countries. Although Gore Viabahn Stent Graft is associated with a very low risk of stent fracture, lifestyle habits, such as sitting on the heels, in Japan that are different from the US and Europe may affect the safety and efficacy of Gore Viabahn Stent Graft. For this reason, this study was conducted. No stent fracture was reported by Month 12. The incidence of stent fracture with Gore Viabahn Stent Graft was not higher than that at Month 12 with the approved SFA stents in Japan, thus, the sample size of 250 patients for the use-results surveys is reasonable as with the approved products. The risk of "stent thrombosis" can also be fully assessed with this sample size.

PMDA's view:

The Kaplan-Meier estimate of assisted-primary patency rate up to 760 days (as of [redacted], [redacted]) was 83.3% in this study (Table 14). As shown in Table 17, the primary patency rate at Year 2 in the clinical studies that treated long-segment lesions was 63.1%. In a publication[33] that summarizes the results of the treatment with Gore Viabahn Stent Graft up to Year 3 in 70 patients (mean target lesion length 17.4 ± 7.0 cm; including TASC II Type C or D, 84%), the primary patency rate, defined as no re-stenosis or occlusion of the target lesion as confirmed by ultrasonography, was 73% at Year 1, 64% at Year 2, and 58% at Year 3. In these clinical studies, the outcome after Year 2 was as low as approximately 60% because of a poor outcome at Year 1 compared with that in this study. Since the sample size of this study was limited and the above long-term outcome has been reported overseas, a use-results survey should be conducted to collect the post-marketing safety information of Gore Viabahn Stent Graft on long-segment lesions in the clinical setting in Japan. On the basis of such newly available information, appropriate measures must be taken. In particular, information should be collected on the occurrence of stent fracture and stent thrombosis associated with Gore Viabahn Stent Graft in the treatment of lesions >15 cm in length, to which the approved SFA stents are not indicated. For the survey population proposed by the applicant, long-segment lesions should be included in target lesions. In addition,

information on lesions that are the target of the approved SFA stents should be collected. Since this study revealed occlusion and stenosis attributable to a thrombus, etc., thrombosis, TLR, stent occlusion, and stent stenosis, as well as causes and times of onset thereof should be investigated. The type and period of antiplatelet therapy administered to each patient should also be investigated. On the basis of such information, appropriate risk mitigation measures should be taken as necessary. Given the above, PMDA asked the applicant to amend the draft plan of the use-results survey.

The applicant amended the draft plan accordingly and submitted a new draft plan of the use-results surveys in 250 patients with symptomatic PAD with a target lesion ≥15 cm in length for 6 years and 10 months in total (sales preparation period [redacted] months, registration period [redacted] months, follow-up period 5 years, survey form collection/analysis/data lock period [redacted] months).

This study includes a follow-up investigation for 5 years after implantation of Gore Viabahn Stent Graft. The long-term outcome of Gore Viabahn Stent Graft is important. PMDA considered it necessary to add approval condition 1 to ensure the results of follow-up investigation will be reported over time and that appropriate safety measures should be taken.

8. Data Concerning Matters to be Indicated on Instructions for Use Specified in Paragraph 1 of Article 63-2 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

8.A Summary of the data submitted

The applicant submitted instructions for use (draft) based on the "Applications for Marketing Approval for Medical Device" (PFSB Notification No. 1120-5, dated November 20, 2014).

8.B Outline of the review conducted by PMDA

On the basis of the comments from the Expert Discussion, PMDA concluded that there was no particular problem with the information included in the instructions for use at present provided that the necessary precautions are given, as described in "6.B Outline of the review" of "6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare."

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

The medical device application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of 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.

V. Overall Evaluation

Gore Viabahn Stent Graft is a delivery system with a stent graft placed in a delivery catheter. The PMDA's review on Gore Viabahn Stent Graft focused on (1) its efficacy, safety, range of application, and proper use in the post-marketing setting in vascular injury treatment, and (2) its efficacy and safety in vascular patency treatment. PMDA reached the following conclusions based on comments from the Expert Discussion.

(1) Efficacy, safety, range of application, and proper use in the post-marketing setting in vascular injury treatment

The applicant submitted a clinical evaluation report based on 22 publications reporting the treatment of traumatic or iatrogenic vascular injuries to the subclavian, iliac, superior mesenteric, or hepatic artery

with Gore Viabahn Stent Graft or its previous generation Hemobahn. Stent grafts for vascular injury treatment have long been used overseas. In Japan, similar stent grafts are approved for different indications. Since their treatment concept has been established worldwide, whether Gore Viabahn Stent Graft can be evaluated on literature data was discussed. The feasibility of clinical studies in vascular injuries is low. In Japan, there are high medical needs for stent grafts for peripheral vascular injuries because no such stent graft is available. Gore Viabahn Stent Graft, which is positioned as a life-saving device, will provide great benefits. Given this, the efficacy and safety of Gore Viabahn Stent Graft could be evaluated based on literature data on successful placement at target sites in peripheral blood vessels and successful hemostasis, provided that nonclinical tests confirmed the delivery performance to the target sites and a certain level of sealing performance.

Only a limited number of patients (n = 33) were reviewed in the publications. According to the publications, 32 patients (97.0%) achieved primary hemostasis, including patients who required additional treatment. However, the actual hemostasis success rate can be lower than the reported figure due to publication bias. Nevertheless, these publications verified that there are at least a certain number of cases with successful hemostasis. The safety evaluation of Gore Viabahn Stent Graft revealed occlusion-related adverse events. However, Gore Viabahn Stent Graft was not associated with re-hemorrhage or death. Taking into consideration the comments from the Expert Discussion, PMDA concluded that these adverse events are clinically acceptable because the main trunk is closed to achieve hemostasis in vascular injury treatment. Nonclinical results of Gore Viabahn Stent Graft have shown the basic performances required for stent grafts, including delivery performance and hemostasis performance. Given this and considering the lack of approved peripheral stent grafts, it is of significance to make Gore Viabahn Stent Graft available in clinical practice. However, the long-term safety of Gore Viabahn Stent Graft has not been fully obtained. Gore Viabahn Stent Graft is intended to be used for emergency life-saving purposes. This must be clarified in the instructions for use. Sufficient observations are required after temporary hemostasis is achieved, which must also be included in the instructions for use.

To minimize the risk of treatment with Gore Viabahn Stent Graft in the post-marketing setting, physicians who have sufficient knowledge about the anatomical requirements of vascular injury sites should select appropriate treatment methods and devices including conventional therapies, and physicians who have sufficient experience in addressing problems, such as unsuccessful hemostasis and complications, should use Gore Viabahn Stent Graft. The proposed post-marketing measures included thorough training of treating physicians and a measure to ensure the compliance to the guideline for proper use planned to be prepared by the Japan IVR. Since currently no prospective clinical data are available and a very limited number of cases have been reviewed in the publications, the following use-results survey of Gore Viabahn Stent Graft should be conducted to collect relevant information in the clinical setting: A survey for 5 years in total (sales preparation period [redacted] months, registration period [redacted] years, follow-up period 1 year, survey form collection/analysis/data lock period [redacted] months) in 30 patients with a traumatic or iatrogenic vascular injury to a thoracic, abdominal, or pelvic artery with a reference vessel diameter of 4.0 to 12.0 mm, excluding injuries to the aorta, coronary artery, brachiocephalic artery, carotid artery, vertebral artery, and pulmonary artery. On the basis of such newly available information, appropriate measures must be taken.

(2) Efficacy and safety in vascular patency treatment

The applicant submitted clinical data from a Japanese single-arm clinical study of Gore Viabahn Stent Graft used to improve blood flow in patients with symptomatic PAD. Gore Viabahn Stent Graft is proposed to be indicated for the treatment of TASC II Type C or D lesions, whose currently recommended first-line treatment is surgical bypass. The performance goal in this study was chosen

with reference to the results of surgical bypass. The majority of the patient population of this study were patients who were candidates for surgical bypass and had slightly mild clinical symptoms. This study showed an assisted-primary patency rate of 91.0% and a clinical success rate, defined as ≥1 improvement in Rutherford category at 12 months post-procedure, of 90.9% (90 of 99 patients). On the basis of these results, PMDA verified the efficacy of Gore Viabahn Stent Graft, as an endovascular treatment device, in the treatment of longer-segment lesions than those treated with the approved products. However, this study enrolled no patients with Rutherford category ≥4 or patients with severe calcification, for both of whom surgical bypass is indicated, and included only 10 patients with TASC II Type D lesions. Given these points and considering the evidence in the guidelines, etc., there are not sufficient grounds for concluding that Gore Viabahn Stent Graft can substitute surgery in the treatment of all TASC II Type C or D lesions, whose current first-line treatment is surgery. Gore Viabahn Stent Graft is less invasive than surgical bypass. However, the safety evaluation showed stent graft occlusion and stenosis likely caused by stent thrombosis. Gore Viabahn Stent Graft has a covered stent structure, unlike conventional SFA stents. Gore Viabahn Stent Graft is used in longer lesions than those that are treated with conventional stents. Given these points and considering that Gore Viabahn Stent Graft has a characteristic of heparin-bonding layer, the recommended duration of DAPT in the post-marketing setting must be clarified. Considering the risk of the prolonged use of DAPT with Gore Viabahn Stent Graft compared with that with conventional metal stents used to treat lesions in the SFA, it is essential to make decisions on whether to use Gore Viabahn Stent Graft after fully assessing its risk-benefit balance. This should be included in the instructions for use. In addition, the following use-results survey should be conducted to collect information regarding adverse events, such as stent fractures and stent thrombosis, etc. in long-segment lesions: A survey in 250 patients with symptomatic PAD with a target lesion ≥15 cm in length for 6 years and 10 months in total (sales preparation period [redacted] months, registration period [redacted] months, follow-up period 5 years, survey form collection/analysis/data lock period [redacted] months). On the basis of newly available information, appropriate risk mitigation measures must be taken.

As a result of its review, PMDA has concluded that Gore Viabahn Stent Graft may be approved for the intended use as shown below.

Intended Use

Gore Viabahn Stent Graft is indicated for emergency treatment of patients who have blood leakage that is difficult to manage due to a traumatic or iatrogenic injury to the thoracic, abdominal, or pelvic artery with a reference vessel diameter of 4.0 to 12.0 mm, excluding injuries to the aorta, coronary artery, brachiocephalic artery, carotid artery, vertebral artery, and pulmonary artery.

In addition, Gore Viabahn Stent Graft is indicated for improving blood flow in patients with symptomatic peripheral arterial disease having a ≥10 cm lesion in the SFA with a reference vessel diameter ranging from 4.0 to 7.5 mm.

Approval Conditions

Treatment of traumatic or iatrogenic vascular injuries

1. The applicant is required to ensure that the product is used by physicians with a full understanding of the efficacy and safety of the product, as well as adequate knowledge and experience in treating traumatic or iatrogenic vascular injuries to the arteries in the chest, abdomen, or pelvis in compliance with the approved indications of the product. For this purpose, the applicant must take necessary measures to ensure that physicians follow the guidelines for proper use of the product prepared in collaboration with relevant academic societies and take necessary educational programs.

2. The applicant is required to take necessary measures in cooperation with related academic societies to ensure that the product is used by physicians who meet the requirements in 1 above at medical institutions capable of taking necessary measures in the event of an emergency including stent graft-related complications.

Vascular patency treatment

1. The applicant is required to report to the Pharmaceuticals and Medical Devices Agency the results of a periodic analysis of long-term prognosis in patients participating in the submitted clinical study and take appropriate measures.

Gore Viabahn Stent Graft is designated as a medical device subject to use-results surveys. The duration of the use-results surveys should be 5 years for vascular injury treatment, and 6 years and 10 months for vascular patency treatment. Gore Viabahn Stent Graft is classified as a biological product.

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

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