Review Report

February 5, 2008

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following medical device submitted for registration are as follows.

[Category]	Instrument & Apparatus 7　Organ function replacement device
[Generic name]	Aortic stent grafts
[Brand name]	GORETAG Thoracic Aortic Stent Graft System
[Applicant]	Japan Gore-Tex Inc.
[Date of application]	November 6, 2006
[Reviewing office]	Office of Medical Devices

Review Results

February 5, 2008

[Category] Instrument & Apparatus 7 Organ function replacement device

[Generic name] Aortic stent grafts

[Brand name] GORETAG Thoracic Aortic Stent Graft System

[Applicant] Japan Gore-Tex Inc.

[Date of application] November 6, 2006

[Results of review]

The GORE TAG Thoracic Aortic Stent Graft System (GORE TAG device) consists of the stent-graft for thoracic aortic aneurysm application and the delivery catheter, which is used to prevent further growth and possible rupture of the aneurysm. The stent-graft is placed inside a thoracic aortic aneurysm located between the left subclavian artery and the celiac artery to seal off the aneurysm from blood circulation. The stent-graft is composed of a polytetrafluoroethylene (PTFE) graft that is supported by a self-expanding nitinol stent and the delivery catheter system is used to deliver the stent-graft to the target site.

Non-clinical studies of the GORE TAG device were performed, and in addition to the results of physicochemical tests required for stent-grafts and delivery systems, the results from the studies with the normal thoracic aortas of [redacted] evaluating the safety and efficacy of the device during and after implantation were submitted. In a foreign, non-randomized, non-blinded, controlled clinical study of the GORE TAG repair vs. open surgical repair (234 patients, 17 sites, the US), the primary safety endpoint of the clinical study, the incidence of adverse events through 1 year post-treatment, was significantly lower in the stent-graft repair group (42%) than in the surgical control group (77%) and the primary efficacy endpoint of the clinical study, the proportion of subjects treated with the GORE TAG device free from a device-related adverse event, was 94%, which demonstrated the efficacy and safety of the GORE TAG device in clinical use. Based on overall evaluation of the submitted study data, it has been concluded that the product may be approved.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the intended use as described below, with the

following conditions, and that the application should be deliberated at the Committee on Medical Devices and In-vitro Diagnostics.

[Intended use]

The GORE TAG Thoracic Aortic Stent Graft System is intended for treatment of aneurysms of the thoracic aorta in patients who meet all of the following anatomical requirements:

- Adequate iliac/femoral access
- Proximal and distal aortic neck inner diameters between 23 and 37 mm
- Proximal aortic neck length of ≥ 20 mm distal to either the left subclavian artery or left common carotid artery
- Distal aortic neck length of ≥ 20 mm proximal to the celiac axis

[Conditions for approval]

1. Conduct use-results surveys among all device-treated patients enrolled during the re-examination period to observe the long-term outcomes of the enrolled patients up to 5 years post-implantation and report the results of analysis over time.
2. Report the results of analysis over time up to 5 years post-implantation for patients treated in the clinical studies submitted.
3. Take necessary measures to ensure that the GORE TAG device is used by physicians who fully understand the efficacy and safety of the device through attending the training program on endovascular treatment of thoracic aortic aneurysms with the device and have adequate knowledge and experience in the procedure etc.
4. Take necessary measures to ensure that the GORE TAG device is used at medical institutions where emergency surgery for resection of a thoracic aortic aneurysm with prosthetic graft replacement is available.

Review Report

February 5, 2008

I. Product for Review

[Category]	Instrument & Apparatus 7　Organ function replacement device
[Generic name]	Aortic stent grafts
[Brand name]	GORETAG Thoracic Aortic Stent Graft System
[Applicant]	Japan Gore-Tex Inc.
[Date of application]	November 6, 2006
[Proposed intended use]	The GORE TAG Thoracic Aortic Stent Graft System is intended for treatment of aneurysms of the thoracic aorta in patients who meet the following anatomical requirements: ・ Adequate iliac/femoral access ・ Proximal and distal aortic neck inner diameters between 23 and 37 mm ・ Proximal and distal aortic neck lengths of ≥ 20 mm distal to either the left subclavian artery or left common carotid artery

II. Product Overview

The GORE TAG Thoracic Aortic Stent Graft System (GORE TAG device) consists of the stent-graft for thoracic aortic aneurysm application and the delivery catheter, which is used to prevent further growth and possible rupture of the aneurysm. The stent-graft is placed inside a thoracic aortic aneurysm located between the left subclavian artery and the celiac artery to seal off the aneurysm from blood circulation. The stent-graft is composed of a polytetrafluoroethylene (PTFE) graft that is supported by a self-expanding nitinol stent and the delivery catheter system is used to deliver the stent-graft to the target site.

Delivery catheter

(Stent-graft on the leading end)

Stent-graft (when unconstrained)

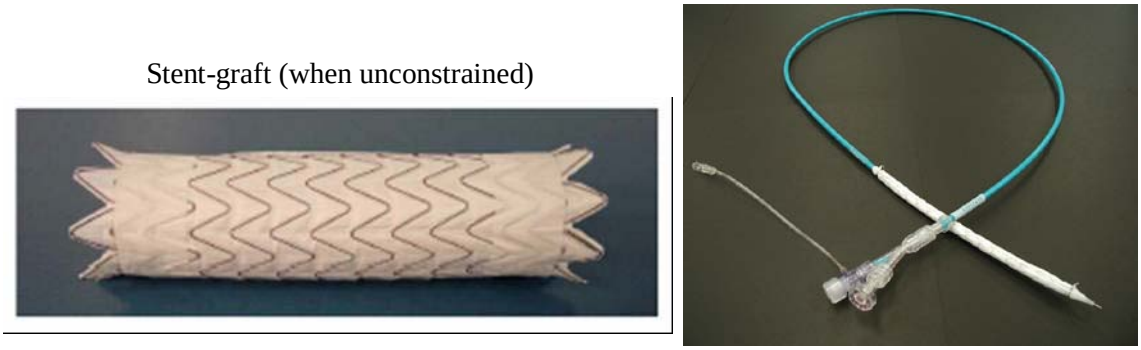


Figure 1. Appearance of stent-graft

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

With regard to this application, the data submitted by the applicant and the applicant's responses to the questions from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

[Origin or history of discovery]

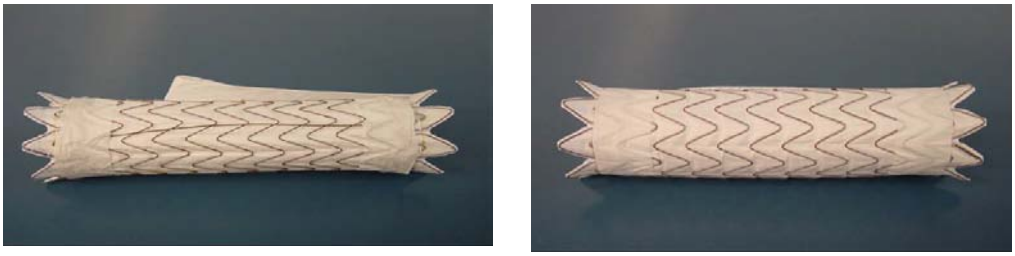
An aneurysm is a fusiform or saccular bulge that develops due to high blood pressure in a weakened area of an artery wall caused by arteriosclerosis etc. Aneurysms commonly occur in the abdominal aorta or thoracic aorta. Most aneurysms remain asymptomatic, but if an aneurysm grows and ruptures, its prognosis is very serious. A ruptured aneurysm may be accompanied by severe pain, consciousness disturbance, etc., leading to a likely fatal outcome. Thus, it is important to treat aneurysms before rupture. The standard treatment for patients with a thoracic aortic aneurysm involves thoracotomy with surgical resection of the diseased aorta and replacement with prosthetic graft material. However, the incidence of complications and mortality associated with open surgical repair are still high although they have been declining recently. Also, it takes a long time to return to normal daily activities after open surgery, which imposes a heavy burden on patients. On the other hand, endovascular placement of stent-grafts is a less invasive method as compared to conventional surgical repair since thoracic aortic aneurysms are treated by implanting stent-grafts via a catheter. Furthermore, it is also expected to enable treatment of patients at high surgical risk.

Historically, after Parodi et al. reported the first clinical use of a stent-graft to treat an abdominal aortic aneurysm in 1991, research and development for the treatment of aneurysms with stent-grafts were undertaken by not only clinicians but also companies. Consequently, stent-grafts for treatment of abdominal aortic aneurysms and stent-grafts for treatment of thoracic aortic aneurysms were commercialized one after another. In Japan, a stent-graft for treatment of aneurysms in the abdominal aorta was first approved in 2006.

The manufacturer of the GORE TAG Thoracic Aortic Stent Graft System, W. L. Gore & Associates, Inc. (the US) initiated the development of stent-grafts for aneurysm repair in 1994 and began distribution of a stent-graft for treatment of abdominal aortic aneurysms in the US in 2002 and in Japan in 2007 ("EXCLUDER Bifurcated Stent Graft System" [Approval Number, 21900BZY00011000]). The GORE TAG Thoracic Aortic Stent Graft System has been submitted for registration in Japan as the first stent-graft that can be used for treating a thoracic aortic

aneurysm, and the product has been marketed in the US since 2005. The GORE TAG Thoracic Aortic Stent Graft System is very similar in materials and structure to “EXCLUDER Bifurcated Stent Graft System.”

In the development of a stent-graft for treatment of thoracic aortic aneurysms, a clinical study with TAG 1.0, a prototype of the GORE TAG device, was conducted in the US, but stent-wire fractures were observed during the follow-up period of the study. In order to address the fracture problem, the design of the stent-graft was modified. Such modification included the removal of the longitudinal spine wire, and a modified version of the device, i.e., TAG 1.5 (the current device design) was developed (Figure 2).



TAG 1.0 TAG 1.5

Figure 2. The original device design (TAG 1.0) and the modified device design (TAG 1.5)

[Usage conditions in foreign countries]

TAG 1.0 first received the CE mark approval for the treatment of aneurysms of the thoracic aorta in European countries in February 1998 and then the modified GORE TAG device received PMA approval from the US FDA in March 2005 and began to be distributed. As of January 2008, approximately 20 000 devices have been used worldwide.

[Occurrence of device-related events in foreign countries]

As of January 2008, the following device-related events have been reported from the post-marketing experience of 20 501 devices used: 198 Type I endoleaks (leaks occurring at the proximal or distal end of the graft immediately after placement) (0.97%); 40 Type II endoleaks (leaks caused by retrograde flow from collateral vessels) (0.20%); 37 Type III endoleaks (leaks arising from defects etc. in the graft itself) (0.18%); 27 indeterminate endoleaks (0.13%); 15 stent-graft migrations (0.07%); 46 unplanned occlusions of branch vessels (0.22%); 16 device breaks (0.08%); and 13 post-procedure aneurysm ruptures (0.06%).

2. Setting of specifications

The product specifications have been established as follows:

The specifications for the stent-graft include surface, stent-wire Af value, water leak test, bend radius, radial force, MRI safety, radiopacity, and biological safety tests, the specifications for the delivery catheter include catheter tensile strength, catheter tensile bond strength, compatibility with guidewire, catheter leak test, and biological safety tests, and the specifications for the entire delivery system include surface, endotoxins, sterility assurance, delivery system release force, compatibility with introducer sheath, deployment system tensile strength, deployment reliability, radiopacity, and biological safety tests.

PMDA reviewed and accepted the above specification data.

3. Stability and durability

Since the delivery catheter of the product uses materials that have never been approved except for the deployment line, the data to ensure the stability of the delivery catheter were submitted. As the current version of the GORE TAG device uses the same delivery catheter as TAG 1.0, the delivery catheter of TAG 1.0 was used as a sample. In stability testing using real-time samples stored for [redacted] years, whether [redacted] required for clinical use is appropriately exhibited was evaluated via [redacted] test. Basically, [redacted] testing using real-time samples should assure the performance of the product after long-term storage, but [redacted] etc. were supplementarily evaluated by stability testing using [redacted].

PMDA determined that the applicant's view that the long-term stability of the product has been assured is appropriate and accepted it because the stability testing using real-time samples showed no problems and the accelerated conditions for stability testing using accelerated aged samples were largely appropriate and it was determined that the expiration period should be estimated from this test data.

4. Conformity to the standards specified in Paragraph 3 of Article 41 of the Pharmaceutical Affairs Law

The declaration of conformity declaring that the product meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare pursuant to Paragraph 3 of Article 41 of the Pharmaceutical Affairs Law (hereinafter referred to as "Essential Principles") (MHLW Ministerial Notification No. 122 of 2005) was submitted.

5. Performance

[Tests to support safety]

As the data from tests to support the safety of the product, the results of physicochemical tests

and biological safety tests using the product as a sample were submitted.

Physicochemical tests performed on the delivery catheter include catheter leak test, catheter tensile bond strength test, catheter torsional strength test, radiopacity confirmation test, deployment line/knob assembly tensile strength test, endovascular system deployment force test, endovascular system deployment reliability test, endovascular system non-destructive dimensional testing, endovascular system simulated use test, and sewn sleeve burst strength test. Physicochemical tests performed on the stent-graft include radiopacity confirmation test, bending fatigue test, bend radius test, burst strength test, cyclic corrosion test, dimensions test, finite element analysis, *in vitro* ultrafiltration test, tensile strength test, MRI safety evaluation, determination of the luminal surface structure, pulsatile fatigue test, radial force test, separation force, water permeability test, simulated use test, graft material abrasion test, graft material water entry pressure testing, and nitinol material analysis test. All the submitted test results met the product specifications.

PMDA asked the applicant to explain the following points concerning the tests to support the safety of the product.

1. In response to stent-wire fractures observed during the follow-up period of a clinical study with TAG 1.0, the device design has been modified. Explain why the applicant thought that such fractures can be prevented by design modifications.
2. The equivalence of the modified version of the GORE TAG device and TAG 1.0 needs to be demonstrated in order to assure the clinical efficacy and safety of the modified device using the results from a clinical study with TAG 1.0. Explain that the modified device performs equivalently to or better than TAG 1.0.
3. As the longitudinal spine wire was removed after design modifications, there is a concern that the modified device may have a reduced longitudinal resistance to compression. Explain the influence of the design modifications on the compression resistance.
4. It is envisaged that overlapped GORE TAG stent-grafts will be used in angulated segments. Explain the efficacy and safety of overlapped devices in clinical use.

The applicant responded to the above instructions as follows:

1. The following three major design modifications were made: (a) the spine wire was removed, (b) the wire frame was bonded to the graft material in a uniform manner with a bonding tape, and (c) the graft structure was modified.

   (a) The spine wire was removed in order to eliminate the risk of contact fatigue between the spine wire and the wire-frame, which seemed associated with wire fractures. (b) The

wire frame was bonded to the graft material in a uniform manner with a bonding tape in order to reduce the risk of wire fractures. Although it is considered that the risk of wire fractures can be reduced by these modifications, there was a concern that the removal of the spine wire may reduce the longitudinal resistance to compression. To address the concern, (c) the graft was modified from [redacted] to [redacted] structure in order to maintain the longitudinal resistance to compression. These modifications can reduce the risk of wire fractures identified in the original version of the device and can also prevent a decrease in performance associated with the removal of the spine wire.

2. Physicochemical testing, pre-clinical testing using [redacted], etc. were performed on the modified device, and the test results were compared to those for TAG 1.0. As a result, in all testing, the modified device provided equivalent or improved outcomes as compared to TAG 1.0. Thus, the modified device should perform equivalently to or better than TAG 1.0.
3. Testing characterizing the longitudinal resistance to compression was performed on the modified device and TAG 1.0, which demonstrated that the compression resistance of the modified device was equal to or greater than that of TAG 1.0. The results of this testing indicate that there are no problems with the compression resistance of the modified device.
4. By [redacted] and measuring [redacted], the fixation effectiveness of the overlap region of stent-grafts was determined. As a result, the current version of the device was demonstrated to have equivalent or better [redacted] than TAG 1.0. The major performances required for overlapped stent-grafts are sealing in the overlapping portion of devices and the migration resistance of the stent-graft. While the physical properties of the stent-graft that determine these performances are fixation effectiveness, including radial force and flexibility, it is difficult to confirm the efficacy and safety of overlapped devices under various conditions (e.g. the morphology of angulated segments, pulsatile movement of the vessel) in a non-clinical study. Thus, the efficacy and safety of overlapped devices should be determined based on the results from clinical studies conducted in accordance with the guideline for overlapping devices (an overlap by at least 5 cm for the same diameter, an overlap by at least 3 cm for different diameters). In the Pivotal Study (more than one device was implanted in 55% [76 of 137 subjects]) and Confirmatory Study (more than one device was implanted in 67% [34 of 51 subjects]), no Type III endoleaks were reported and there was only 1 report of stent-graft migration in the Pivotal Study. Also from a comprehensive viewpoint, since these clinical studies have demonstrated the efficacy and safety of the GORE TAG device, we consider that the safety of overlapped

devices has also been confirmed.

Taking account of comments from the Expert Discussion, PMDA accepted the applicant's view that the current version of the GORE TAG device modified from TAG 1.0 has at least equivalent performance to TAG 1.0 and a reduction in the risk of wire fractures, the concept of the design modifications, has been achieved. While the clinical studies have provided an assurance of the short-term efficacy and safety of the stent-graft, its long-term efficacy and safety have not been confirmed. Therefore, PMDA has concluded that it is necessary to evaluate 5-year data from post-marketing use-results surveys.

In order to evaluate the biological safety, the delivery catheter which uses materials that have never been approved was tested for cytotoxicity, pyrogenicity, sensitization, irritation/intracutaneous reactivity, acute systemic toxicity, and hemocompatibility in accordance with the ISO 10993 standard and all test results showed no problems. The stent-graft component was not tested again since it uses the same materials as the device already on the market, "EXCLUDER Bifurcated Stent Graft System (Approval Number, 21900BZY00011000)" and the conditions of use including the duration of contact with blood are comparable between these devices.

PMDA reviewed and accepted the data from the tests to support the safety of the product, taking also account of comments from the Expert Discussion.

[Tests to support performance]

In order to support the performance of the product, pre-clinical testing where the devices were implanted in the normal thoracic aortas of [redacted] was conducted to evaluate [redacted], [redacted], [redacted] and [redacted] of the stent-graft component and the results of [redacted], [redacted], and [redacted] evaluated at [redacted] and [redacted] months [redacted] were submitted. All devices were successfully deployed and no particular problems were noted up to 6 months of follow-up. Therefore, the applicant considers that the GORE TAG device has appropriate [redacted] and shows good functionality and biocompatibility of the device when implanted in the normal thoracic aorta have been confirmed. PMDA determined that the applicant's view is appropriate and accepted it.

6. Risk analysis

Regarding the in-house rules of risk management in accordance with ISO 14971:2000 "Application of Risk Management to Medical devices," the data summarizing the applicant's

organizational structure and standard operating procedures were attached. There have so far been no reports of hazards against which safety measures were requested by the MHLW or overseas regulatory agencies etc. with respect to the GORE TAG device and stent-grafts for treatment of thoracic aortic aneurysms.

PMDA reviewed and accepted the risk analysis data.

7. Manufacturing method

As to the manufacturing method, the data on Sterility Assurance Level and in-process tests were submitted, which showed that these tests have been performed appropriately to meet the product specifications and assure the quality.

PMDA reviewed and accepted the data on the manufacturing method.

8. Clinical data

Clinical data from the Pivotal Study with TAG 1.0 and Confirmatory Study with the current version of the GORE TAG device were submitted. The results from the Feasibility Study with TAG 1.0 were submitted as reference data.

The Feasibility Study was a pilot study to evaluate the safety, deployment accuracy, and deployment reliability of TAG 1.0, and its safety (device failures and device-related adverse events) and efficacy (prevention of growth and rupture of aneurysms by restoration of the luminal diameter and maintenance of patency after stent-graft placement) were evaluated in 28 patients with thoracic aortic aneurysms (maximum outer diameter≥ 4 cm or ≥1.5 times the diameter of normal aorta, proximal and distal landing zones of ≥2.0 cm, and proximal and distal aortic neck inner diameters between 23 and 37 mm). As a result, there were no particular problems with its efficacy and safety, which warranted further investigation in a larger clinical study.

[Pivotal Study]

The Pivotal Study (234 patients, 17 sites, the US), which was a multi-center clinical study, was conducted to compare the safety of endovascular repair with TAG 1.0 to open surgical repair and assess the efficacy of TAG 1.0 in the primary treatment of thoracic aortic aneurysms. This clinical study was a non-randomized, non-blinded study that enrolled patients who met TAG 1.0 group inclusion/exclusion criteria (140 patients) or surgical control group inclusion/exclusion criteria (94 patients). The surgical control group included historical controls (patients who had

undergone open surgical repair of a thoracic aortic aneurysm at participating centers and met surgical control group inclusion/exclusion criteria were identified and enrolled). The target disease was specified as thoracic aortic aneurysm deemed to warrant surgical repair (saccular aneurysm or fusiform aneurysm ≥2 times the diameter of normal adjacent aorta) and patients in the TAG 1.0 group had to meet the following anatomical criteria for endovascular repair: (a) aortic neck inner diameter between 23 and 37 mm, (b) lack of significant thrombus and/or calcification in the proximal or distal aortic implantation sites, (c) a minimum of 2 cm non-aneurysmal segment proximal and distal to the aneurysm as a landing zone.

The primary safety endpoint for this clinical study was defined as the occurrence of major adverse events through 12 months post-treatment and the safety was evaluated based on the hypothesis that the proportion of subjects who experienced ≥1 major adverse event was less in the TAG 1.0 group than in the surgical control group. The primary efficacy endpoint was defined as the occurrence and severity of device-related events through 12 months post-treatment in order to assess the device's ability to seal off the aneurysm from the blood flow. The efficacy was evaluated based on the hypothesis that the proportion of patients free from a device-related event through 12 months post-treatment would be ≥80%, assuming that the success rate in sealing off the aneurysm is 80% in the primary treatment of thoracic aortic aneurysms with TAG 1.0. The usefulness was evaluated by comparing procedural blood loss, length of intensive care unit stay, length of hospital stay, and the time to return to normal daily activities, as the secondary endpoints, between the TAG 1.0 group and the surgical control group. Subjects were to be assessed at pre-treatment, post-treatment, hospital discharge, and 1, 3, 6, 12, 24, 36, 48, and 60 months and follow-up data through 24 months were submitted at the time of filing the application.

Study results

1. Safety evaluation

The primary safety endpoint: major adverse events through 12 months post-treatment are shown in Table 1. The proportion of patients who experienced≥ 1 major adverse event through 12 months post-treatment was significantly lower in the TAG 1.0 group (42%) compared to the surgical control group (77%) (P < 0.001, Fisher's exact test), which confirmed that endovascular repair of thoracic aortic aneurysms with TAG 1.0 is safer than open surgical repair through 12 months post-treatment. Concerning the incidence of major adverse events by organ system through 12 months post-treatment, the incidence of major bleeding, pulmonary, renal, wound, and neurological complications was significantly lower in the TAG 1.0 group while the incidence of major vascular complications (e.g. thrombosis, vascular trauma) was higher in the

TAG 1.0 group (18% vs. 6%, P = 0.011). Six TAG 1.0 subjects (4%) required reoperation (implantation of an additional TAG 1.0) to treat the aneurysm through 12 months post-treatment.

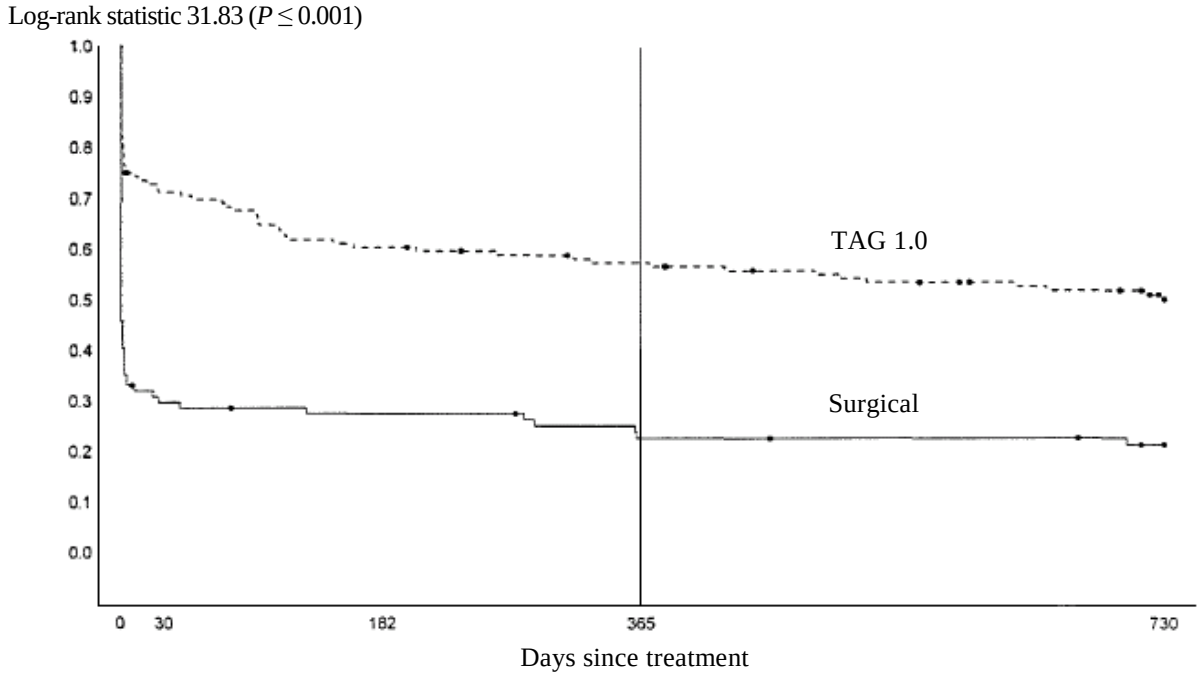
Twenty-four-month follow-up data from this study were submitted and the majority of adverse events were observed within 1 month post-treatment in both groups. The proportion of patients free of a major adverse event through 24 months post-treatment remained higher in the TAG 1.0 group than in the surgical control group (Figure 1).

Table 1. The primary safety endpoint: major adverse events through 12 months post-treatment

Safety endpoints	TAG 1.0 (N = 140) n (%)	Surgical control (N = 94) n (%)	Estimated risk difference[1] (95% CI)	*P*-value[2]
Any major adverse event	59 (42)	72 (77)	34 (21.72, 47.18)	< 0.001
Bleeding complications (e.g. coagulopathy, haematoma)	16 (11)	51 (54)	43 (30.57, 55.08)	< 0.001
Pulmonary complications	18 (13)	36 (38)	25 (13.27, 37.61)	< 0.001
Cardiac complications	22 (16)	22 (23)	8 (-3.67, 19.05)	0.17
Renal function complications	6 (4)	14 (15)	11 (1.78, 19.44)	0.007
Wound complications	9 (6)	14 (15)	8 (-0.69, 17.62)	0.043
Bowel complications	6 (4)	6 (6)	2 (-4.76, 8.96)	0.55
Vascular complications (e.g. thromboembolism, vascular trauma)	25 (18)	6 (6)	-11 (-20.40, -2.54)	0.011
Neurological complications	15 (11)	31 (33)	22 (10.58, 33.95)	< 0.001
Other major complications	2 (1)	3 (3)	2 (-3.19, 6.71)	0.39
Aortoenteric fistula	0	1 (1)		
Graft infection	2 (1)	2 (2)		
Reoperation[3]	6 (4)	0	(0.57, 8.00)	
Deaths from other or unknown causes[4]	11 (8)	5 (5)	-3 (-9.79, 4.71)	0.6

Note: Column headers and denominators are the number of subjects enrolled.
The reported start date before Day 365 was used for analysis.
[1] *Risk difference is the rate in the surgical control group minus the rate in the TAG 1.0 group.*
[2] *P-values are based on Fisher's exact test.*
[3] *The confidence interval is based on the point estimates for the TAG 1.0 group only.*
[4] *Deaths from specific documented major adverse events are included in the respective adverse event categories. All other deaths are included in this category.*

Figure 1. Subjects free of a major adverse event through 24 months post-treatment



No difference between the TAG 1.0 (24%, 34 of 140 subjects) and surgical control (26%, 24 of 94 subjects) groups was noted in all-cause mortality through 2 years post-treatment [see Figure 2]. Aneurysm-related mortality was lower in the TAG 1.0 vs. surgical control groups (3% vs. 10%, P = 0.04) [see Figure 3]. No device-related deaths were noted through 2 years post-treatment.

Figure 2. All-cause mortality through 2 years post-treatment

Log-rank statistic 0.50 (P = 0.48)

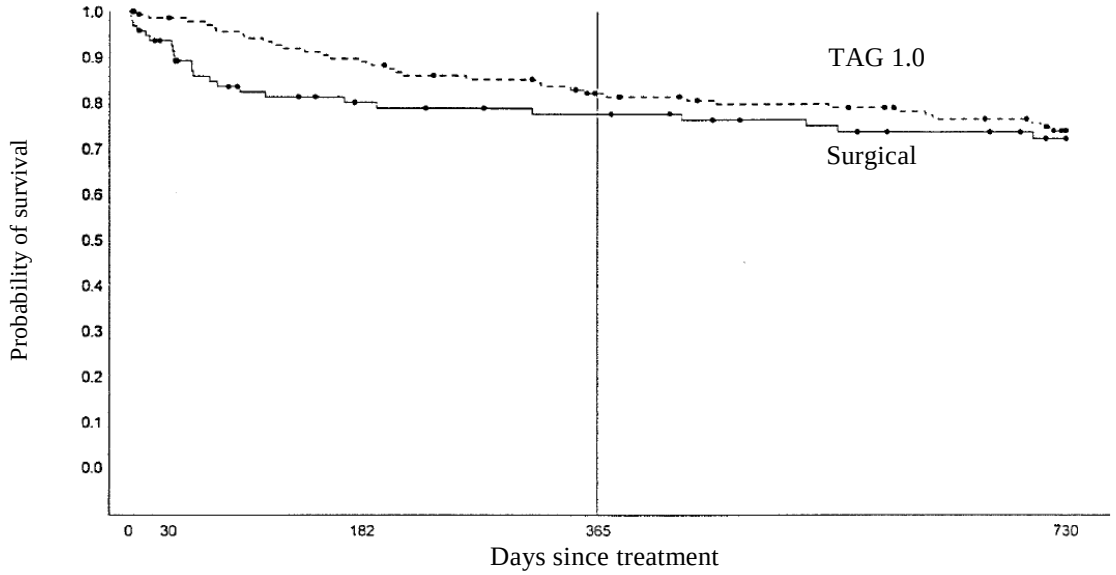
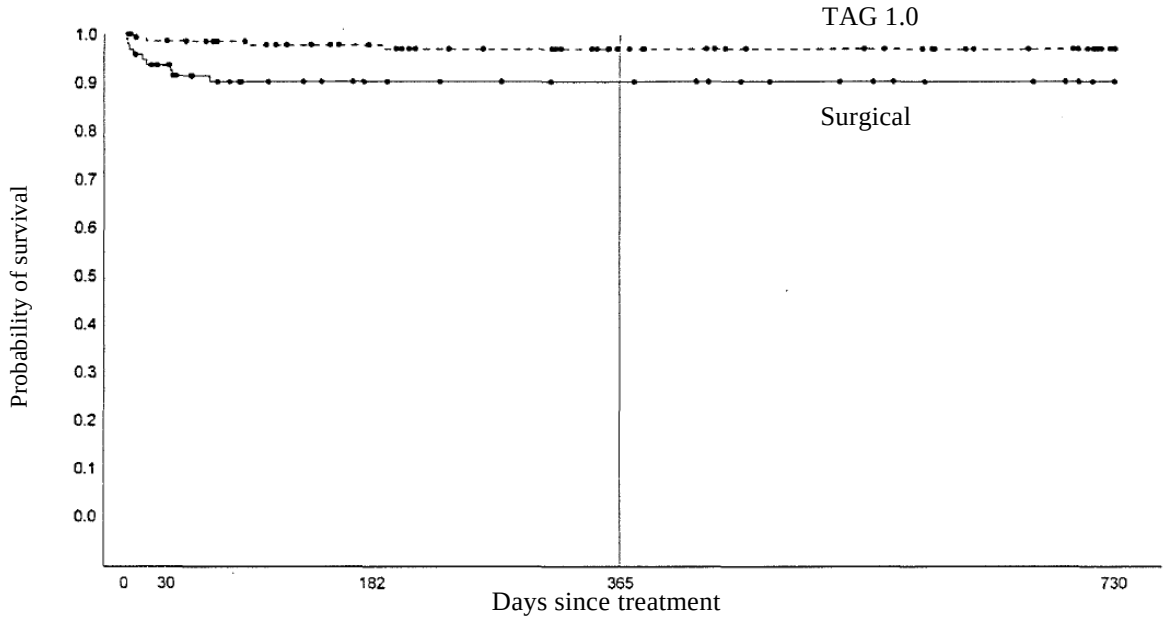


Figure 3. Aneurysm-related mortality through 2 years post-treatment

Log-rank statistic 5.11 (P = 0.024)



2. Efficacy evaluation

The primary efficacy endpoint, the proportion of patients treated with TAG 1.0 free from a major device-related event through 12 months post-treatment was 94% (8 subjects [6%] experienced ≥1 major device-related event). If one assumes that all 10 subjects without a 12-month follow-up visit had a major device-related event in this period, the proportion of patients free from a major device-related event was 87.1%, which confirmed the efficacy of TAG 1.0. Device-related events reported include 3 cases of Type I endoleak (2%), 1 case of branch vessel occlusion (1%), 1 case of graft migration (1%), 2 cases of treatment-related device event (1%), and 3 cases of aneurysm enlargement ≥ 5 mm (2%). No aneurysm ruptures were noted through 2 years post-treatment (Table 2).

Table 2. Efficacy endpoint: major device-related events through the 12-month follow-up visit

Major device-related events[1]	TAG 1.0 (N = 140) n (%)	95% confidence interval
Any major device-related event	8 (6)	(1.51, 9.92)
Endoleak	4 (3)	(0.00, 5.97)
Type I	3 (2)	
Ia	3 (2)	
Ib	0	
Type II	0	
Type III	0	
Type IV	0	
Indeterminate	1 (1)	
Aneurysm rupture	0	
Treatment-related device event (e.g., deployment failure)	2 (1)	(0.00, 3.75)
Unplanned occlusion of a branch vessel	1 (1)	(0.00, 2.47)
Lumen obstruction	0	
Graft migration	1 (1)	(0.00, 2.47)
Graft realignment	0	
Graft material failure	0	
Aneurysm enlargement[2]	3 (2)	(0.00, 4.90)
Other device complication after treatment	0	

Note: Column header and denominators are the number of subjects enrolled.

12-month follow-up visit is defined as 241 to <548 days or 8 to <19 months.

[1] All events are based on the Sacks criteria for a major event.

[2] Aneurysm enlargement is based on a ≥ 5-mm change from the size at the Month 1 visit.

3. Usefulness evaluation

In order to evaluate the clinical benefit of the TAG 1.0 device, comparisons were made between the TAG 1.0 and surgical control groups for secondary endpoints, i.e., blood loss during procedure, length of intensive care unit stay, length of hospital stay, and the time to return to

normal daily activities. The TAG 1.0 group had shorter median intensive care unit (1 day in the TAG 1.0 group vs. 3 days in the surgical control group, $P < 0.001$, Wilcoxon rank sum test) and hospital (3 days in the TAG 1.0 group vs. 10 days in the surgical control group, $P < 0.001$, Wilcoxon rank sum test) stays [see Table 3]. Although no test of significance was performed for procedural blood loss and the time to return to normal daily activity due to a high proportion of missing data, the TAG 1.0 group experienced less blood loss and returned to normal daily activities sooner as compared to the surgical control group, suggesting that the TAG 1.0 group had improved clinical benefit over the surgical control group.

Table 3. Secondary endpoints

Endpoint	TAG 1.0 (N = 140)	Surgical control (N = 94)	*P*-value[1]
Blood loss during procedure (ml [cm^3])	N = 133	N = 52	
Mean ± SD	472.1 ± 859.4	2402 ± 2719	□
Length of ICU stay (days)	N = 137	N = 91	
Mean ± SD	2.6 ± 14.6	5.2 ± 7.2	< 0.001
Length of hospital stay (days)	N = 140	N = 91	
Mean ± SD	7.4 ± 17.7	14.4 ± 12.8	< 0.001
Time to return to normal daily activities (days)	N = 114	N = 51	
Mean ± SD	60.2 ± 82.7	149.2 ± 201.0	□

Note: Column headers are the number of subjects enrolled.
[1] *P-values are based on Wilcoxon rank sum test.*
□ *No test of significance due to high proportion of missing data.*

[Confirmatory Study]

During the follow-up period, wire fractures were identified in stent-grafts implanted in 19 patients (longitudinal spine wire fractures and wire-frame fractures in the region where the wires were not bonded to the underlying graft material). In order to solve this problem, the aforementioned design modifications were made and the current version of the GORE TAG device was developed.

The Confirmatory Study, which was a multi-center, non-randomized, uncontrolled study (11 sites, 51 patients), was conducted to confirm that the modified device has equivalent clinical performance to the original TAG 1.0 device. A 30-day safety endpoint was chosen based on the following facts: (a) the majority of major adverse events occurred within 30 days post-treatment in the Pivotal Study and (b) 1-year data from the Pivotal Study demonstrated a significant difference in the incidence of major adverse events between the TAG 1.0 and surgical control groups within 30 days post-treatment.

The Confirmatory Study used the same inclusion/exclusion criteria as the Pivotal Study so as to compare safety and efficacy data between the Confirmatory Study (subjects treated with the current GORE TAG device) and Pivotal Study (the surgical control and TAG 1.0 groups).

The primary endpoint was defined as the occurrence of major adverse events through 30 days post-treatment and the safety was evaluated based on the hypothesis that the proportion of subjects who experienced ≥1 major complication through 30 days post-treatment was less in the subjects treated with the current GORE TAG device than in the surgical control group of the Pivotal Study (94 patients). The secondary endpoint was defined as the occurrence and severity of device-related events through 30 days post-treatment to assess the device's ability to seal off the aneurysm from the blood flow and the efficacy was evaluated by comparing with the 30-day data from the TAG 1.0 group (139 patients) of the Pivotal Study. Usefulness evaluation was also conducted in the same manner as the Pivotal Study. One-year follow-up data (follow-up rate, 86%) as well as 30-day data (the primary endpoint) from the Confirmatory Study were reported.

The test group (subjects treated with the current GORE TAG device) of the Confirmatory Study is referred to as the TAG 1.5 group.

Study results

1. Safety evaluation

Major adverse events in the Confirmatory Study (within 30 days post-treatment) are shown in Table 4. The proportion of patients who experienced ≥1 major adverse event through 30 days post-treatment was significantly less in the TAG 1.5 group (12%) compared to the surgical control group (70%) ($P < 0.001$, Fisher's exact test). None of the subjects in the TAG 1.5 group died during the 30-day follow-up period.

The incidence of major adverse events occurring during the period ranging from >30 days to 1 year post-treatment was 12%, which showed no particular problems.

Table 4. Major adverse events in the Confirmatory Study, 0 to 30 days

				Estimated risk difference[1] (95% CI)	
Safety endpoint	TAG 1.5 (N = 51) n (%)	TAG 1.0 (N = 139) n (%)	Surgical control (N = 94) n (%)	TAG 1.5 vs. TAG 1.0 [2]	TAG 1.5 vs. Surgical control [3]
Any major adverse event	6 (12)	39 (28)	66 (70)	16 (3.38, 29.21)	58 (44.14, 72.75)**
Bleeding complications (e.g. coagulopathy, haematoma)	0	13 (9)	50 (53)	9 (3.17, 15.53)	53 (41.59, 64.79)**
Pulmonary complications	2 (4)	9 (6)	31 (33)	3 (-5.50, 10.61)	29 (16.65, 41.46)**
Cardiac complications	1 (2)	4 (3)	19 (20)	1 (-5.14、6.97)	18 (7.77, 28.73) **
Renal function complications	0	2 (1)	12 (13)	1 (-1.88, 4.76)	13 (4.51, 21.02)**
Wound complications	1 (2)	8 (6)	11 (12)	4 (-2.97, 10.56)	10 (0.70, 18.78)*
Bowel complications	0	3 (2)	6 (6)	2 (-1.60, 5.91)	6 (-0.07, 12.84)
Vascular complications (e.g. thromboembolism, vascular trauma)	3 (6)	19 (14)	4 (4)	8 (-2.17, 17.75)	-2 (-10.78, 7.52)
Neurological complications	1 (2)	11 (8)	30 (32)	6 (-1.27, 13.18)	30 (18.28, 41.63)**
Other major complications	0	0	1 (1)		1 (-2.52, 4.65)
Graft infection	0	0	1 (1)		
Reoperation[4]	1 (2)	4 (3)	0	1 (-5.14, 6.97)	(0.00, 6.75)
Deaths from other or unknown causes[5]	0	2 (1)	1 (1)	1 (-1.88, 4.76)	1 (-2.52, 4.65)

Note: Column headers and denominators are the number of subjects enrolled.
The reported start date before Day 30 was used for analysis.
[1] *P-values are based on one-sided Fisher's exact test.*
[2] *Risk difference is the rate in the TAG 1.0 group (Pivotal Study) minus the rate in the TAG 1.5 group (Confirmatory Study). 95% confidence intervals are two-sided.*
[3] *Risk difference is the rate in the surgical control group (Pivotal Study) minus the rate in the TAG 1.5 group (Confirmatory Study). 95% confidence intervals are two-sided.*
[4] *The confidence interval for the TAG 1.5 group (Confirmatory Study) vs. the surgical control group (Pivotal Study) is based on the point estimates for the TAG 1.5 group (Confirmatory Study) only.*
[5] *Deaths from specific documented major adverse events are included in the respective adverse event categories. All other deaths are included in this category.*

2. Efficacy evaluation

One subject (2%) in the TAG 1.5 group and 6 subjects (4%) in the TAG 1.0 group had device-related events through 30 days post-treatment, which showed no statistically significant difference. Two subjects (4%) in the TAG 1.5 group had device-related events during the period ranging from >30 days to 1 year, which include 1 case of Type I endoleak and 1 case of planned occlusion of the subclavian artery.

3. Usefulness evaluation

Comparisons were made between the TAG 1.5 group and the TAG 1.0 group or the surgical control group for procedural blood loss, length of intensive care unit stay, length of hospital stay, and the time to return to normal daily activities. The TAG 1.5 group had shorter mean intensive care unit stay (1.2 days in the TAG 1.5 group vs. 5.2 days in the surgical control group; $P < 0.001$, t-test) and hospital stay (4.8 days in the TAG 1.5 group vs. 14.4 days in the surgical control group; $P < 0.001$, t-test) compared to the surgical control group. In addition, the TAG

1.5 group experienced less procedural blood loss and shorter time to return to normal daily activities than the surgical control group. The data from this study demonstrated the improved clinical benefit of TAG 1.5.

PMDA asked the applicant to explain why the results from clinical studies conducted in the US without a Japanese clinical study can ensure the efficacy and safety of the GORE TAG device in Japanese patients.

The applicant responded as follows:
As treatment with the GORE TAG device is indicated only for patients who meet specific criteria including the anatomical requirements, relevant clinical study data can be evaluated regardless of local subject characteristics. Although it has been reported that Japanese patients are small in body size and their aortic diameters are also slightly smaller, many of the Japanese patients meet an anatomical requirement for the application of the GORE TAG device, i.e., aortic neck inner diameters in the range of 23 to 37 mm, and the GORE TAG device is available in sizes suitable for Japanese patients as well.

In Japan, treatment of thoracic aortic aneurysms generally involves thoracotomy. According to the 2004 data collected by the Japanese Association for Thoracic Surgery, the overall in-hospital mortality among 4299 patients treated for non-dissecting aneurysms of the thoracic aorta has been reported to be 9.2%. Based on the anatomical requirements for the use of the GORE TAG device, eligible patients should have an aneurysm involving a part of the distal aortic arch or the descending aorta and their estimated in-hospital mortality is approximately 5.8% to 13.6%. In the US clinical study, the mortality in the surgical control group was 6% at 30 days post-surgery and 10% at 2 years post-surgery, which were similar to the in-hospital mortality in Japan. Therefore, the results from the US clinical study that demonstrated the safety and efficacy of the GORE TAG device as compared to open surgical repair can be extrapolated into the Japanese clinical setting.

Furthermore, as to stent-graft implantation procedure, a stent-graft for treatment of an abdominal aortic aneurysm has already been approved; therefore, as with the stent-graft for aneurysms of the abdominal aorta, the medical institutions' qualifications for performing this procedure will be specified and treating physicians will be required to attend the training program. In light of these points, no major problems are anticipated when introducing this procedure into the clinical practice.

As described above, since (a) the anatomical requirements for the use of the device have been specified and the device is available in sizes suitable for Japanese patients as well, (b) the outcomes of in-hospital mortality in the surgical control group from the Pivotal Study are similar to the outcomes of in-hospital mortality after surgical repairs in Japan, and (c) an abdominal stent-graft has been approved and physicians' qualifications for using the device, e.g. attendance at the training program, will be specified, treatment of thoracic aortic aneurysms in medical practice is similar between Japan and the US. Thus, we have judged that the results from the US clinical study can be extrapolated into the Japanese population.

PMDA considered as follows:
Although the applicant's view on the appropriateness of extrapolation of the US clinical study data into the Japanese population is acceptable, as with a stent-graft for treatment of abdominal aortic aneurysms, for safer use of the GORE TAG device, physicians familiar with thoracic aortic aneurysms should fully understand the characteristics of the device and then attend the training program to use the device. Therefore, it is necessary to impose the following condition for approval: "Take necessary measures to ensure that the GORE TAG device is used by physicians who fully understand the efficacy and safety of the device through attending the training program on endovascular treatment of thoracic aortic aneurysms with the device and have adequate knowledge and experience in the procedure etc. (Condition for approval 3)" In addition, since conversion to emergency surgery for resection of a thoracic aortic aneurysm with prosthetic graft replacement will be required if the aneurysm is injured during the implantation procedure of the device, it is necessary to impose the following condition for approval: "Take necessary measures to ensure that the GORE TAG device is used at medical institutions where emergency surgery for resection of a thoracic aortic aneurysm with prosthetic graft replacement is available. (Condition for approval 4)"

The GORE TAG device is placed inside an aneurysm of the thoracic aorta, but the vascular morphology etc. varies at different implantation sites and the performance required of the device should differ accordingly. PMDA asked the applicant to explain the following points on whether the GORE TAG device can provide adequate performance at likely implantation sites.

1. Explain the method of risk assessment in the case where occlusion of the left subclavian artery is required and the necessary measures to ensure safer treatment.
2. Check whether the efficacy and safety of the device differ according to the implantation site (different zones, angulated or non-angulated segment, the degree of angulation) and the morphology of aneurysm.
3. Provide a justification for requiring a ≥ 2-cm landing zone.

The applicant responded to these instructions as follows:

1. While occlusion of the left subclavian artery to obtain an adequate landing zone for stent-graft placement is considered one of the common procedures for treatment of thoracic aortic aneurysms with a stent-graft, there is no consensus about the risk associated with occlusion of the left subclavian artery and the necessity of preserving the blood flow. Prior to the use of the GORE TAG device, it is necessary to assess the risk associated with occlusion of the left subclavian artery preoperatively and consider taking actions, including discontinuation of treatment. Therefore, the following caution statement will be included in the instructions for use: "If occlusion of the left subclavian artery is required to use the GORE TAG device, the risk associated with occlusion should be assessed preoperatively. Then if preserving the blood flow of the left subclavian artery is essential, treatment should be discontinued or transposition of the left subclavian artery etc. to preserve the blood flow should be considered."
2. Because the information on the zone of the implantation site was not collected, the zones where stent-grafts were implanted could not be identified. However, since at least the group [redacted] had the stent-graft implanted in zone 2, patients were divided into two groups according to whether it was implanted in zone 2 or other sites. The efficacy and safety of the device was evaluated for each group and there were no differences in the outcomes between the groups. The degree of angulation could not be measured using the collected imaging data, but based on [redacted], the implantation sites of stent-grafts were identified. As a result, in this clinical study, the implantation sites were not localized to specific regions, but were well distributed over the thoracic aorta distal to the left subclavian artery and proximal to the celiac artery, which is the intended anatomic location for the placement of the GORE TAG device. There were no differences in the occurrence of adverse events among the distributions and there should be no major difference in the efficacy and safety of the device among different implantation sites. When aneurysms were classified as fusiform or saccular to evaluate the efficacy and safety of the device, no difference was noted. Thus, the morphology of aneurysm does not significantly affect the efficacy and safety of the device.
3. Although a ≥2-cm landing zone has been specified for the GORE TAG device, the length of the landing zone for the actually implanted stent-grafts was not measured in the clinical studies and nor could be determined from the collected imaging data. As it was difficult to directly measure the landing zone lengths, assuming that patients with [redacted] of ≤ [redacted] cm had a landing zone of only approximately [redacted] cm [redacted], the clinical data were compared between patients with [redacted] of ≤ [redacted] cm and the others. As a result, there were no differences in the outcomes according to the neck

length. Taking account of the fact that the Pivotal Study and Confirmatory Study were conducted in accordance with this anatomical requirement and the consideration from the standpoint of the neck length, a ≥2-cm landing zone can be justified.

The location of implantation of a GORE TAG stent-graft ranges widely from the distal arch to the segment proximal to the celiac artery, but in any case, basically, determining an adequate normal aortic landing zone is important. Concerning the applicant's view on the appropriateness of a ≥2-cm landing zone, when taking account of the clinical studies conducted in accordance with this anatomical requirement and the clinical usage in foreign countries, PMDA does not deny a ≥ 2-cm landing zone. Meanwhile, it is necessary to collect information via post-marketing use-results surveys and carefully determine its appropriateness based on the results from long-term efficacy and safety analysis. As the description of the neck length in the Intended Use and Indications section: "Proximal and distal aortic neck lengths of ≥20 mm distal to either the left subclavian artery or left common carotid artery" is not clear about the distal neck length proximal to the celiac axis, proximal and distal neck lengths should be described separately in a clear manner. For the use of the GORE TAG device, all of the anatomical requirements listed in the Intended Use section need to be met. Thus, PMDA determined that the wording in the Intended Use and Indications section should be modified so as to make this point clear.

Since there are no long-term clinical outcomes even though endovascular treatment with a stent-graft is effective in the short term, PMDA considers that its long-term efficacy and safety have not been confirmed at present. PMDA asked the applicant to explain the long-term efficacy and safety of the GORE TAG device.

The applicant responded as follows:
Four-year follow-up data from the Pivotal Study showed similar incidences of major adverse events for each group: major adverse events occurred in 15 of 108 subjects (14%) in the TAG 1.0 group and 7 of 64 subjects (11%) in the surgical control group during the period ranging from >12 months to 24 months, 8 of 89 subjects (9%) in the TAG 1.0 group and 4 of 54 subjects (7%) in the surgical control group during the period ranging from >24 months to 36 months, and 6 of 75 subjects (8%) in the TAG 1.0 group and 3 of 37 subjects (8%) in the surgical control group during the period ranging from >36 months to 48 months. Similarly, mortality occurred in 43 subjects (30%) in the TAG 1.0 group and 30 subjects (32%) in the surgical control group through 4 years post-treatment. The efficacy endpoint, i.e., major device-related events were noted in 3 subjects during the follow-up period ranging from >12 months to 24 months and

there were no major device-related events during the follow-up period ranging from >24 months to 48 months. Based on the above, 4-year follow-up data from the Pivotal Study also suggest that the GORE TAG stent-graft is a safe and effective medical device.

Since there is no clinical experience with the GORE TAG device in Japan and no long-term outcomes have been available even in foreign countries, PMDA determined that the following conditions for approval should be imposed: “Conduct use-results surveys among all device-treated patients enrolled during the re-examination period to observe the long-term outcomes of the enrolled patients up to 5 years post-implantation and report the results of analysis over time. (Condition for approval 1)” and “Report the results of analysis over time up to 5 years post-implantation for patients treated in the clinical studies submitted. (Condition for approval 2)”

Taking account of comments from the Expert Discussion, PMDA accepted the applicant’s view that the above clinical study data provide an assurance of the efficacy and safety of the GORE TAG device.

IV. Results of Compliance Review by PMDA Concerning the Documents Appended to the Application

[Results of the document conformity audit and GCP document compliance review and on-site inspection]

A document conformity audit was conducted in accordance with the provision of Paragraph 5 of Article 14 of the Pharmaceutical Affairs Law for the documents appended to the application. As a result, there were no problems. A document compliance review for foreign clinical studies was also conducted and there were no problems. Therefore, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted documents.

[Results of the QMS document compliance review and on-site inspection]

A compliance review was conducted in accordance with the provision of Paragraph 6 of Article 14 of the Pharmaceutical Affairs Law. As a result, PMDA concluded that there were no particular problems.

V. Overall Evaluation

The GORE TAG device is a stent-graft system, which is placed inside an aneurysm of the thoracic aorta via a catheter to prevent blood from flowing through the aneurysm. In response to wire fractures observed during the follow-up period of the Pivotal Study that is an important study in terms of ensuring the clinical efficacy and safety of the device, the original design of the stent-graft has been modified to develop the current version of the device. Since unlike open surgery with prosthetic graft replacement, endovascular repair of a thoracic aortic aneurysm with a stent-graft is not curative, not only the short-term performance but also the long-term efficacy and safety of the device must be demonstrated. Therefore, the major points in the review were as follows: (1) The current version of the GORE TAG device performs equivalently to or better than the original TAG 1.0 device and the appropriateness of evaluating the clinical efficacy and safety of the current device using the results from a clinical study with TAG 1.0, (2) The long-term efficacy and safety of the GORE TAG device, (3) Development of a system for education and training etc. necessary to ensure the effective and safe use of the GORE TAG device, and (4) Judgment on whether the GORE TAG device should be used for the treatment of thoracic aortic aneurysms. Taking account of comments from the Expert Discussion on these points, PMDA determined as follows:

(1) In response to wire fractures observed in the Pivotal Study, the spine wire was removed, the wire frame stent was bonded to the graft material in a uniform manner with a bonding tape, and the graft structure was modified. Physicochemical, deployment performance, and implant performance tests and pre-clinical testing in [redacted] were conducted on the current version of the GORE TAG device. Test results were compared to TAG 1.0, including an assessment of the influence of these modifications on the performance characteristics. As a result, the modified device basically performed equivalently to or better than TAG 1.0. Although the longitudinal resistance to compression may be affected by the removal of the spine wire, it has been demonstrated that the compression resistance of the modified device is equal to or greater than that of TAG 1.0. Based on the above, the current version of the GORE TAG device performs equivalently or better than TAG 1.0 and evaluation using the results from a clinical study with TAG 1.0 is appropriate.

(2) Early results from the clinical study have shown no particular problems with the current version of Gore TAG stent-grafts that were implanted in angulated segments with adequate landing zones as per the protocol. Although the outcomes at >1 year post-implantation have not been available, since fatigue/durability test performed under stress conditions demonstrated that favorable outcomes were maintained and the current version of the GORE TAG device has equivalent performance to TAG 1.0, there has been no cause for

concern about the long-term efficacy and safety of the device at present. However, due to the characteristics of the device, malfunctions can cause serious health injuries. Therefore, as it is necessary to collect the long-term outcomes of the GORE TAG device and conduct a 5-year follow-up post-marketing surveillance study in order to confirm the long-term efficacy and safety of the device in Japanese patients, the following conditions for approval should be imposed: “Conduct use-results surveys among all device-treated patients enrolled during the re-examination period to observe the long-term outcomes of the enrolled patients up to 5 years post-implantation and report the results of analysis over time. (Condition for approval 1)” and “Report the results of analysis over time up to 5 years post-implantation for patients treated in the clinical studies submitted. (Condition for approval 2)”

(3) In order to fully make the most of the product performance and use the device more safely, the GORE TAG device should only be used by fully educated and trained physicians. Also, if an aneurysm is injured during the implantation procedure of the device, it will be necessary to perform open surgery with prosthetic graft replacement promptly. Therefore, the following two conditions for approval should be imposed: “Take necessary measures to ensure that the GORE TAG device is used by physicians who fully understand the efficacy and safety of the device through attending the training program on endovascular treatment of thoracic aortic aneurysms with the device and have adequate knowledge and experience in the procedure etc. (Condition for approval 3)” and “Take necessary measures to ensure that the GORE TAG device is used at medical institutions where emergency surgery for resection of a thoracic aortic aneurysm with prosthetic graft replacement is available. (Condition for approval 4)”

(4) Although the GORE TAG device is considered an effective therapeutic approach, there have been no long-term follow-up clinical data. Thus, the following caution statement should be included in the instructions for use so that physicians will more carefully determine whether or not the GORE TAG device should be used: “When considering the use of the GORE TAG device, the physician should fully assess the patient’s risk factors with the hospital staff who perform surgical and drug treatment of thoracic aortic aneurysms and then make a comprehensive decision, exploring other treatment options.”

Based on the above results, PMDA has concluded that the product may be approved after modifying the intended use as shown below. However, as it is important to carefully observe the long-term outcomes of the GORE TAG device and collect information, the following conditions for approval need to be imposed.

[Intended use]

The GORE TAG Thoracic Aortic Stent Graft System is intended for treatment of aneurysms of the thoracic aorta in patients who meet all of the following anatomical requirements:

- Adequate iliac/femoral access
- Proximal and distal aortic neck inner diameters between 23 and 37 mm
- Proximal aortic neck length of≧ 20 mm distal to either the left subclavian artery or left common carotid artery
- Distal aortic neck length of ≥20 mm proximal to the celiac axis

[Conditions for approval]

1. Conduct use-results surveys among all device-treated patients enrolled during the re-examination period to observe the long-term outcomes of the enrolled patients up to 5 years post-implantation and report the results of analysis over time.
2. Report the results of analysis over time up to 5 years post-implantation for patients treated in the clinical studies submitted.
3. Take necessary measures to ensure that the GORE TAG device is used by physicians who fully understand the efficacy and safety of the device through attending the training program on endovascular treatment of thoracic aortic aneurysms with the device and have adequate knowledge and experience in the procedure etc.
4. Take necessary measures to ensure that the GORE TAG device is used at medical institutions where emergency surgery for resection of a thoracic aortic aneurysm with prosthetic graft replacement is available.

As the GORE TAG Thoracic Aortic Stent Graft System is a new medical device, the appropriate re-examination period should be 3 years. The product is not classified as a biological product or a specified biological product.

The application should be deliberated at the Committee on Medical Devices and In-vitro Diagnostics.