Report on the Deliberation Results

December 7, 2012
Office of Medical Device Evaluation
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Classification	Instrument & Apparatus 7 Organ function replacement device
Term Name	Aortic stent graft
Brand Name	Kawasumi Najuta Thoracic Stent Graft System
Applicant	Kawasumi Laboratories, Incorporated
Date of Application	August 10, 2011 (Application for marketing approval)

Results of Deliberation

In the meeting held on December 7, 2012, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and concluded that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The Committee discussed the content of Condition of Approval 1 shown below, and concluded that the Condition should include a statement to the effect that appropriate measures should be taken when using the product in the area of the aortic arch branch vessels.

The Committee's conclusion:
The product may be approved with a re-examination period of 3 years under the following conditions of approval. The product is not classified as a biological product or a specified biological product.

Conditions of Approval

1. The applicant is required to take appropriate measures to ensure that the product is used by physicians with sufficient knowledge and experience in endovascular repair of thoracic aortic aneurysms (including the area of the aortic arch branch vessels) at medical institutions able to provide treatment of possible complications of endovascular stent graft repair.

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.

2. The applicant is required to take appropriate measures to ensure that the product is used only for the indication by qualified physicians (i.e., those who meet the criteria specified in Condition of Approval 1) who, through training, etc., have acquired sufficient skills in maneuvering the product and sufficient knowledge of complications of the procedures.
3. The applicant is required to perform use-results surveys (including an extension survey of patients participating in the submitted clinical trial) covering all patients treated with the product until data from a specific number of patients have been accrued; report the results of long-term outcome analysis to the Pharmaceuticals and Medical Devices Agency; and take appropriate measures as necessary.

Review Report

November 13, 2012

Pharmaceuticals and Medical Devices Agency

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

Classification	Instrument & Apparatus 7　Organ function replacement device
Term Name	Aortic stent graft
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Reviewing Office	Office of Medical Devices I

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Review Results

November 13, 2012

Classification	Instrument & Apparatus 7　Organ function replacement device
Term Name	Aortic stent graft
Brand Name	Kawasumi Najuta Thoracic Stent Graft System
Applicant	Kawasumi Laboratories, Incorporated
Date of Application	August 10, 2011

Results of Review

Kawasumi Najuta Thoracic Stent Graft System (Najuta Stent Graft) is a stent graft system for the treatment of thoracic aortic aneurysm consisting of a stainless-steel stent (Z stent skeleton) and a polytetrafluoroethylene (PTFE) graft ([redacted]) sewn on the stent. The stent graft is loaded into the delivery sheath in advance.

Najuta Stent Graft offers 64 basic types (shapes) of stent skeletons with different lengths, curves, and torsion angles, to allow selection of the optimal one for the site and shape of affected aorta of each patient. A straight or tapered graft, with or without a fenestration(s), that matches the expanded aortic diameter is sutured and fixed to the stent skeleton. Accordingly, 952 variations result from various combinations of grafts and stent skeletons.

In a Japanese clinical trial in patients with true or false aneurysm of the aortic arch or descending aorta, Najuta Stent Graft was shown to be non-inferior to open surgery (historical control data) in the primary endpoint of "survival rate at 12 months after aneurysm-related treatment." This result demonstrates the efficacy of Najuta Stent Graft.

The trial showed no substantial differences in the safety endpoint of "incidence of major complications" between Najuta Stent Graft and open surgery (historical control data). Thus, at present, there are no safety problems with Najuta Stent Graft.

It is required to choose a type of Najuta Stent Graft from 952 types by selecting a stent skeleton, curve, and the number of fenestrations suitable for the aneurysm. The applicant should therefore examine whether the suitable type is selected properly for individual patients in routine clinical practice after the market launch. The post-marketing surveillance should cover all patients receiving Najuta Stent Graft

regardless of fenestration status until information is collected from a certain number of patients. The fenestrated stent grafts, unique to Najuta Stent Graft, are not approved outside Japan, and the Japanese clinical trial have provided only limited data on them; the post-marketing surveillance should therefore focus on their safety and efficacy. The clinical trial has demonstrated the short-term efficacy and safety of Najuta Stent Graft, but has not shown the long-term efficacy or safety. The long-term outcome of patients should therefore be followed up in the post-marketing surveillance.

Najuta Stent Graft should be used by physicians who have been well trained in advance, in order to ensure the proper, efficient and safe use of the device. In addition, prompt surgical interventions should be available in case of aneurysm rupture associated with implantation of Najuta Stent Graft.

Based on its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the intended use shown below with the following conditions, and that this result should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

Intended Use and Indication

Najuta Stent Graft is used in the treatment of thoracic aortic aneurysms that meet all of the following anatomical requirements:

1. An appropriate iliac/femoral artery access route is available.
2. Normal portions of the aorta (without any aneurysm) that meet the following criteria are available as sealing zones at both the proximal and distal sides of an aneurysm:
    - The length of the normal vessel between the bifurcation of the left common carotid artery and the aortic aneurysm is ≥20 mm. (When the left subclavian artery is not covered, the length of the normal blood vessel between the bifurcation of the left subclavian artery and the aortic aneurysm is ≥20 mm.)
    - The length of the normal vessel between the bifurcation of the celiac artery and the aortic aneurysm is ≥20 mm.
    - The normal vessel at the sealing zones of the proximal and distal sides of the aneurysm has a diameter of ≥20 mm and <38 mm.

Conditions of Approval

1. The applicant is required to take appropriate measures to ensure that the product is used by physicians with sufficient knowledge and experience in endovascular repair of thoracic aortic aneurysms at medical institutions able to provide treatment of possible complications of endovascular stent graft repair.
2. The applicant is required to take appropriate measures to ensure that the product is used only for the indication by qualified physicians (i.e., those who meet the criteria specified in Condition of

Approval 1) who, through training, etc., have acquired sufficient skills in maneuvering the product and sufficient knowledge of complications of the procedures.

3. The applicant is required to perform use-results surveys (including an extension survey of patients participating in the submitted clinical trial) covering all patients treated with the product until data from a specific number of patients have been accrued; report the results of long-term outcome analysis to the Pharmaceuticals and Medical Devices Agency; and take appropriate measures as necessary.

Review Report

November 13, 2012

I. Product for Review

Classification	Instrument & Apparatus 7 Organ function replacement device
Term Name	Aortic stent graft
Brand Name	Kawasumi Najuta Thoracic Stent Graft System
Applicant	Kawasumi Laboratories, Incorporated
Date of Application	August 10, 2011

Proposed Intended Use

Kawasumi Najuta Thoracic Stent Graft System is used in the treatment of thoracic aortic aneurysms that meet all of the following anatomical requirements:

1. An appropriate iliac/femoral artery access route is available.
2. Normal portions of the aorta (without any aneurysm) that meet the following criteria are available as sealing zones at both the proximal and distal sides of an aneurysm:
   - The length of the normal vessel between the bifurcation of the left common carotid artery and the aortic aneurysm is ≥20 mm. (When the left subclavian artery is not covered, the length of the normal blood vessel between the bifurcation of the left subclavian artery and the aortic aneurysm is ≥20 mm.)
   - The length of the normal vessel between the bifurcation of the celiac artery and the aortic aneurysm is ≥20 mm.

II. Product Overview

Kawasumi Najuta Thoracic Stent Graft System (Najuta Stent Graft) is a stent graft system for the treatment of thoracic aortic aneurysm. The stent graft consists of a stainless-steel stent (Z stent skeleton) and a polytetrafluoroethylene (PTFE) graft sewn on the stent, and is loaded into a delivery sheath (Figure 1). After being delivered to the target site and released from the delivery sheath, the stent graft is self-expanded to a specified diameter and closely fitted to the inner wall of the blood vessel to prevent blood flow into the aneurysm and subsequent aneurysm rupture due to pressure load.

Najuta Stent Graft offers 64 basic types (shapes) of stent skeletons[1] with different lengths, curves, and torsion angles, to allow selection of the optimal one for the site and shape of affected aorta for each patient. A straight or tapered graft, with or without a fenestration(s) (Figure 2), that matches the expanded aortic diameter is sutured and fixed to the stent skeleton. Accordingly, 952 variations result from various combinations of grafts and stent skeletons.

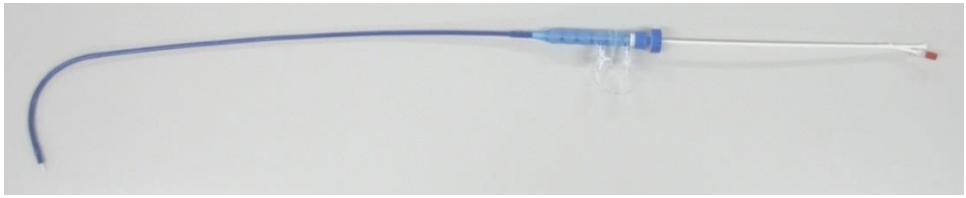
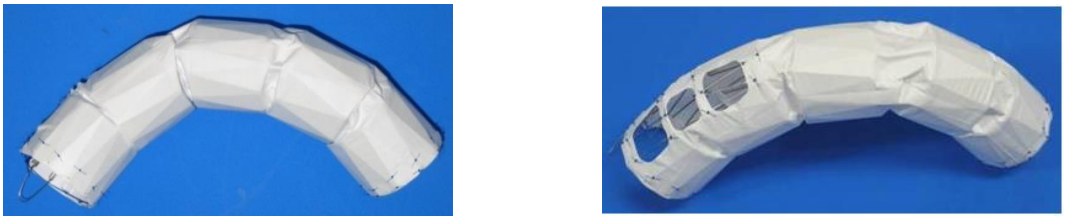


Figure 1. Appearance of stent graft system



Unfenestrated Fenestrated

Figure 2. Appearance of stent graft

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

The data submitted by the applicant for the present application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below. The expert advisors present during the Expert Discussion on this product 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. 8/20 dated December 25, 2008).

1. Origin or history of discovery, use in foreign countries, and other information

1.(1) Origin or history of discovery

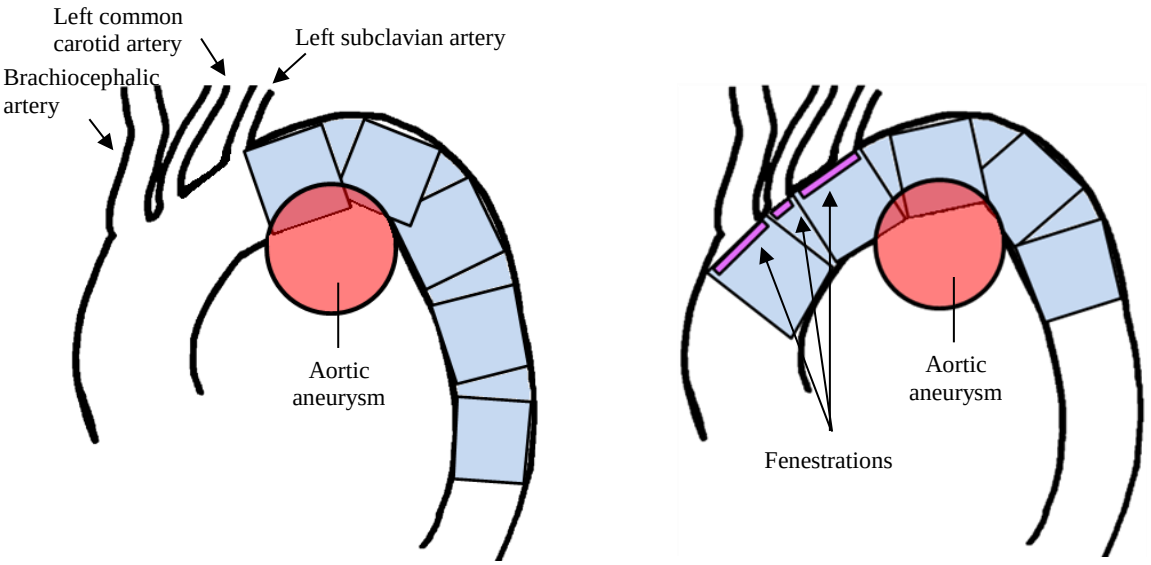
Thoracic aortic aneurysm is a serious disease. If left untreated, it may rupture, which may result in death. The conventional first-line treatment for aortic aneurysm is open surgery, and blood vessel prosthesis implantation used to be the most common treatment. Blood vessel prosthesis implantation requires extracorporeal circulation depending on the location and condition of the aneurysm and causes a large amount of bleeding. Since this open surgery is very invasive, the in-hospital mortality of patients with aortic arch aneurysms, the primary indication of Najuta Stent Graft, is 6% on average, although

[1] With different stent lengths, curves, and torsion angles, there are 16 large arch models, 10 small arch models, 5 arch 4-stent models, 9 descending (large) models, 5 descending (small) models, 9 thoracoabdominal (large) models, 9 thoracoabdominal (small) models, and one 3-stent model.

outcomes of the surgery have been improved according to data from the Japanese association for thoracic surgery. Further, patients undergoing endovascular stent graft repair of thoracic aortic aneurysm (including aortic arch, descending, and thoracoabdominal aneurysms) had an acute mortality of approximately 5% (2%-10%) and an intermediate (5-year) survival of approximately 40% to 87%, showing no substantial difference from those undergoing open surgery.[1] Endovascular stent graft repair is less invasive than conventional surgery because a stent graft is implanted through a catheter, and is expected to enable treatment of patients at high risk for open surgery.

In Japan, GORE TAG Thoracic Aortic Stent Graft System (Approval No. 22000BZX00185000) was approved in March 2008 as the first stent graft for the treatment of thoracic aorta aneurysms. As of September 2012, 4 stent graft systems have been commercially available. However, all of these approved thoracic stent grafts have the problem of occlusion of aortic arch branch vessels (brachiocephalic artery or left common carotid artery) when they are used to treat a thoracic aortic aneurysm close to the branch vessels. To address this problem, stent grafts, including fenestrated ones, have been developed to ensure blood flow into the aortic arch branch vessels. Najuta Stent Graft with 1 to 3 fenestration(s) can be implanted under the aortic arch branch vessels (the brachiocephalic artery, left common carotid artery, and left subclavian artery) by placing the fenestration(s) under the branch vessels close to the target aneurysm. The stent graft therefore does not block blood flow into the branch vessels even when it is placed from the ascending to descending aorta. Implanting a conventional unfenestrated stent graft at the lesser curvature side is difficult because of insufficient sealing zone. Fenestrated stent grafts, however, allow a longer sealing zone and therefore may enable treatment of aneurysms at the lesser curvature side (Figure 3). Najuta Stent Graft offers 64 basic types of stent skeletons with different stent lengths, curves, etc., to allow selection of a stent graft with the curve most similar to the shape of affected blood vessel based on CT images. Consequently, an optimal stent graft can be selected from 952 types according to the expanded diameter of stent, shape (straight or tapered), and the number of fenestrations.

Kawasumi Laboratories, Incorporated conducted a Japanese clinical trial of Najuta Stent Graft, and submitted the marketing application of the device as a stent graft for the treatment of thoracic aortic aneurysm.



A. Similar medical device B. Najuta Stent Graft

Figure 3. Difference in sealing zone due to fenestration status

1.(2) Use in foreign countries

There has not been a marketing application of Najuta Stent Graft outside Japan. The device has not been used outside Japan.

1.(3) Malfunctions associated with Najuta Stent Graft or similar medical devices

There is no experience with Najuta Stent Graft or similar medical devices.

2. Setting of specifications

The following product specifications were proposed at the time of submission with reference of ISO7198:1998 “International standard for cardiovascular implants -Tubular vascular prostheses” and ISO25539-1:2003 “Cardiovascular implants - Endovascular devices - Part 1: Endovascular prostheses” for the stent grafts, and ISO10555-1:1995 “Sterile, single-use intravascular catheters. General requirements” and ISO11070:1998 “Sterile, single-use intravascular catheter introducers” for the delivery sheaths.

The specifications for Najuta Stent Graft include appearance, biological safety, residue on ethylene oxide gas sterilization, endotoxins, sterility assurance level (SAL) and assurance method, specifications for the stent grafts and delivery sheaths, and kink resistance of the stent graft sets. The specifications for the stent grafts include the joint strength of the stent skeleton, graft’s seal strength, pressure resistance, graft’s water permeability, corrosion resistance, radiopacity, MRI safety, deployment completeness, and suture strength between stent skeleton and graft. The specifications for the delivery sheaths include maximum applicable guide wire diameter, hemostatic capability, joint strength, and hydrophilic coating.

As the proposed specifications were not sufficient, PMDA asked the applicant to provide a rationale for the specifications for the performance of the stent grafts and delivery system.

The applicant's response:
"Stent graft migration resistance" and "radial force" will be added to the proposed specifications for the performance of stent grafts, and "stent graft release force" and "longitudinal tensile strength of the tube" to the proposed specifications for the performance of the delivery system.

PMDA asked the applicant to provide a rationale for the acceptance criteria for the "radial force," "graft's water permeability," and "stent's joint strength."

The applicant's response:
In view of the intended use of Najuta Stent Graft, the reference value of the radial force of the stent grafts is ≥[redacted] N, because the value guarantees the self-expanding nature of the stent grafts.

The graft's water permeability was confirmed under the pressure of 120 mmHg (16 kPa) based on ISO7198 8.2.3. The specifications for Najuta Stent Graft require the grafts to be not permeable to water under normal blood pressure (acceptance criteria, [redacted]).

The reference value of the stent's joint strength 60 N, because it is higher than the release force [redacted].

PMDA's view:
Najuta Stent Graft is intended to prevent blood from flowing into aneurysms. To achieve this aim, a stent graft is inserted and implanted in the target artery, and appropriately fitted to the inner wall of the blood vessel. Since Najuta Stent Graft has the same intended use as the conventional products, the basic performance required does not substantially differ from that of the conventional products. The following basic physicochemical performance of stent graft systems, similar to those for the conventional stent grafts, suffice as the specifications for Najuta Stent Graft: The joint strength of the stent graft and delivery sheath, graft's water permeability, radial force, stent graft migration resistance, kink resistance, sheath hemostatic capability, delivery performance, durability, etc. Fenestrated Najuta Stent Graft can be placed from the ascending to descending aorta. In this case, stent graft migration may cause significant safety problems, such as blockage of blood flow to the brachiocephalic artery, common carotid artery, and left subclavian artery. The stent graft migration resistance needs to be comprehensively investigated on the basis of nonclinical and clinical data. In the clinical trial,

intraoperative stent graft migration occurred in 3 of 117 subjects (2.6%), when the stent graft was expended and attached to the aorta using a balloon catheter after deployment of Najuta Stent Graft (2 cases) and when the delivery sheath was caught by the stent skeleton during retracting (1 case). All of the subjects received additional interventions, with neither a stent graft migration nor a clinical problem due to incomplete expansion, damage, etc. at ≥3 months after surgery. Although the physicians should be cautioned about possible stent graft migration during the procedures, the clinical results raise no particular concerns about migration resistance of Najuta Stent Graft.

The nonclinical study to assure the physicochemical performance of Najuta Stent Graft was conducted based on the international standards.[2] The study raised no particular concerns regarding the joint strength of the stent graft and delivery sheath, graft's water permeability, kink resistance, sheath hemostatic capability, etc. The proposed specifications for radial force, graft's water permeability, stent's joint strength, etc. are also appropriate. Since the clinical trial using the product meeting the specifications demonstrated the efficacy and safety of Najuta Stent Graft [see Section "8. Clinical data"], the proposed specifications are acceptable.

Based on the above, PMDA concluded that there were no particular concerns with the proposed specifications.

3. Stability and durability

Najuta Stent Graft was subjected to a 12-month real-time stability study (first run) at 25°C. However, raw materials of some parts ([redacted]) of the delivery sheath were changed, and an additional 12-month real-time stability study (second run) was conducted. The results of the first real-time stability study and the results over the first 6 months of the second real-time stability study were submitted in this submission.

The first stability study parameters included the appearance, dimensions, joint strength of the delivery sheath, longitudinal tensile strength of the tube, leakage, hemostasis valve performance, water permeability, burst (pressure resistance), graft's seal strength, joint strength of the stent skeleton, release force, sterility assurance, and biological properties (acute toxicity, pyrogens, and hemolysis). Between the first and second stability studies, the raw material of the delivery sheath was changed, but no change was made to the stent graft or packaging materials. The second stability study therefore skipped the tests that met the acceptance criteria in the first study and only assessed the appearance, dimensions, joint strength of the delivery sheath, longitudinal tensile strength of the tube, leakage, and hemostasis valve

[2] ISO7198:1998 "International standard for cardiovascular implants - Tubular vascular prostheses." ISO25539-1:2003 "Cardiovascular implants - Endovascular devices - Part 1: Endovascular prostheses." ISO10555-1:1995 "Sterile, single-use intravascular catheters. General requirements." ISO11070:1998 "Sterile, single-use intravascular catheter introducers."

performance. In both studies, all tests met the respective acceptance criteria. On the basis of the above results, the shelf-life of Najuta Stent Graft was determined to be 6 months.

To support the durability of Najuta Stent Graft, the applicant submitted results of a fatigue durability test using a non-overlapping unfenestrated stent graft and overlapping stent grafts (between unfenestrated and fenestrated ones). In the test, stent grafts were placed in a mock aortic arch [redacted] under mimic physiological conditions (37°C, pH 7.4 phosphate buffered saline, system inner pressure criteria [redacted] ± [redacted] mmHg), and, under accelerated conditions, subjected to approximately 400 million blood vessel pulsations, which corresponds to approximately 10 years of use in the human thoracic aorta. The non-overlapping unfenestrated stent graft was tested for any crack or fracture of the stent graft skeleton, graft pinhole, detachment of the graft layer, suture break, and suture hole break. The overlapping stent grafts (between unfenestrated and fenestrated ones) were tested not only for these parameters but also for graft migration in the mock aortic arch and for detachment of the fenestration part. None of the sample stent grafts had any damage, such as a crack, in the structure or on the surface. The tests demonstrated the durability of Najuta Stent Graft.

PMDA asked the applicant to discuss the appropriateness of sample stent grafts used in the durability test.

The applicant's response:
"Small Arch Stent 5" ([redacted]) was selected as the sample unfenestrated stent graft, because [redacted] model, a stent graft having a complicated shape and the smallest diameter with the largest deformation of the skeleton, was considered to be the worst-case sample with a potentially large displacement. The tests of fenestrated stent grafts were intended to assess the durability of overlapping stent grafts. Accordingly, "Small Arch Stent 5L" was selected as the sample fenestrated stent graft for overlapping, because it had the smallest diameter with the largest deformation of the skeleton and is the longest among [redacted] models. The other overlapping stent graft was "Arch 4-stent 1," placed at the distal side, because it had the same diameter as "Small Arch Stent 5L" but a different [redacted].

The applicant omitted tests of overlapped stent grafts whose diameters were 2 sizes different, although the instructions for use of Najuta Stent Graft allows for placement of several stent grafts having a diameter difference of not more than 2 sizes (4 mm). PMDA asked the applicant to provide a rationale for omitting the tests.

The applicant's response:

The durability assessment of overlapped stent grafts, [redacted]. There appears to be no difference in the stress on the overlapped portion of the stent grafts or in the risk for damage due to friction. In summary, the safety of Najuta Stent Graft can be assured without conducting durability tests of models whose stent graft diameters are 2 sizes different, the largest possible difference.

PMDA's view on the stability and durability:

The real-time stability studies were conducted to evaluate the primary performance-related tests of sample stent grafts and delivery sheath stored for 12 and 6 months, respectively. The results met the acceptance criteria, showing the sustainable stability and performance of Najuta Stent Graft. The proposed shelf-life of 6 months, to ensure the performance of Najuta Stent Graft, is acceptable.

A durability test was conducted under physiological conditions which mimic the actual conditions for implantation of Najuta Stent Graft. In the test, visual inspection and light microscopy revealed no particular dysfunctional crack, fracture, graft pinhole, detachment of the graft layer, suture break, or suture hole break. Najuta Stent Graft has a durability required for thoracic aorta stent grafts. For the test of overlapping stent grafts, the applicant selected the appropriate sample stent grafts and severe conditions that gave the largest possible stress on the overlapped portion of sample stent grafts, based on the structure of the stent skeleton, the results of the radial force test, and the simulation results of a stent stress analysis. In addition, the following explanation by the applicant is acceptable: several Najuta Stent Grafts having a diameter difference of not more than 2 sizes can be implanted simultaneously. PMDA thus concluded that the durability of Najuta Stent Graft was appropriately assessed in the durability test.

4. Conformity to the requirements specified in Paragraph 3 of Article 41 of the Pharmaceutical Affairs Act

The applicant submitted a declaration of conformity declaring that Najuta 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 the Pharmaceutical Affairs Act (hereinafter referred to as "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).

PMDA reviewed the product' conformity to the Essential Principles and accepted the declaration.

5. Performance

5.(1) Studies supporting safety

To support the safety of Najuta Stent Graft, the applicant submitted the results of a physicochemical study and a biological safety study.

5.(1).1) Physicochemical properties

The physicochemical study included tests for residue on ethylene oxide gas sterilization, extractable substances (metal extract), corrosion resistance, radial force, graft's water permeability, effects of MRI, appearance, dimensions, joint strength, longitudinal tensile strength of the tube, leakage, torsion strength, hemostatic capability (hemostasis valve performance), water entry pressure, burst pressure, kink resistance, local compression, joint strength of the stent, joint strength between the graft and stent, stent graft release force, stent graft migration resistance, coating durability, integrity of deployed stet graft, joint strength at the overlapped portions of stent grafts, kink resistance of the delivery sheath, stress analysis (FEM analysis) of stent graft, and endotoxins.

All of these tests met the respective acceptance criteria or showed no abnormality.

5.(1).2) Biological safety

Biological safety was evaluated in accordance with the following:

- "Basic Principles of Biological Safety Evaluation Required for Application for Approval to Manufacture (Import) Medical Devices" (PFSB/ELD Notification No. 0213001 dated February 13, 2003, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW)
- "Reference Materials for Basic Principles of Biological Safety Evaluation" (PFSB/ELD/OMDE Administrative Notice No. 36 dated March 19, 2003, by the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW)
- ISO 10993 series

Tests of stent grafts:

Cytotoxicity, sensitization, genotoxicity (reverse mutation and chromosome abnormality), implantation, intracutaneous reaction, acute toxicity, pyrogen, blood compatibility (hemolytic toxicity), and sub-acute toxicity tests.

Tests of delivery sheaths:

Cytotoxicity, sensitization, intracutaneous reaction, acute toxicity, pyrogen, and blood compatibility (hemolytic toxicity) tests. (These tests used sample sheaths made of the post-change raw materials [see Section "3. Stability and durability"].)

There were no findings suggesting biological safety concerns in any of the tests.

PMDA asked the applicant to explain why Najuta Stent Graft is considered MRI compatible.

The applicant's response:

Najuta Stent Graft was evaluated for MRI compatibility (i.e., magnetic interactions, heat generation, and artifacts) using 1.5 T MRI system. The magnetic interaction test assessed displacement force and torque at a spatial gradient field of 400 Gs/cm, in accordance with ASTM F2052 "Standard test method for measurement of magnetically induced displacement force on passive implants in the magnetic resonance environment" and ASTM F2213 "Standard Test Method for Measurement of Magnetically Induced Torque on Passive Implants in the Magnetic Resonance Environment." No significant problem was identified. In the heat generation test, Najuta Stent Graft was imaged at a specific absorption rate (SAR) of the MR system of 3.77 W/kg for 15 minutes, in accordance with ASTM F2182 "Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging." No significant heat increase was found. The artifact test was conducted in accordance with ASTM F2219 "Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants." Artifacts occurred over the range of 16.5 cm at maximum, suggesting that Najuta Stent Graft may affect MR images.

When the stent graft is implanted in or relatively close to the area of diagnostic imaging, it can reduce MR image quality. PMDA asked the applicant to include a caution about this issue in the package insert. As the applicant took an appropriate measure, PMDA accepted the applicant's response.

In view of the above, PMDA reviewed the studies supporting safety based on the submitted test results and concluded that there was no significant problem.

5.(2) Study supporting the performance of device

In order to evaluate the safety and maneuverability during placement of Najuta Stent Graft, unfenestrated stent grafts (overlapped grafts, 13 animals; single graft, 10 animals) were implanted in the thoracic aorta of 23 Suffolk sheep (17 females, 6 males). The test animals were examined at Months 1 (3 animals), 3 (3 animals), 6 (6 animals), and 12 (4 animals) of placement for aortography, histology, haematology, biochemistry, and others (blood pressure, pulse rate, body temperature [at the start and

end of stent placement surgery and of the surgery conducted at the end of evaluation period], and body weight [immediately before stent graft placement and at the end of evaluation period]). To evaluate the safety, each stent graft was examined for the completeness of placement (position, condition, and angle after placement), size suitability, radiopacity after placement at the completion of stent graft placement; stent's corrosion resistance, stent's physical strength (bent, strut, and joint), graft's physical strength (graft and seal parts), and suture strength of the stent and graft (joint of the stent and graft) after retracting the stent graft; and for thrombosis, occlusion, dissociation, endoleak, stent graft migration, and other adverse events throughout the testing period.

Clinical observation and aortography of animals, and the safety evaluation of the stent grafts showed no concerns.

Histology revealed slight deposition of fibrin-like material around the stent graft, and slight to moderate neointimal formation between the inner wall of the blood vessel and the graft, in the stent graft, or around the stent in all animals. At Months 1, 3, 6, and 12 of placement, however, no inflammatory change was observed in the vascular wall and perivascular tissue. Changes at Month 3 were almost consistent with those at Month 1 of placement. Neointimal formation at Months 6 and 12 was slightly more noticeable than that at Months 1 and 3. Neither marked neointimal nor thrombus formation in the stent grafts was observed throughout the study period, showing no safety concern.

Haematology, clinical chemistry, and the other attributes tested showed a few changes, but no abnormality associated with the test substance.

Some animals had adverse events of breast swelling probably caused by mastitis and swelling at the insertion site probably due to bleeding from the vascular suture site. Other animals showed a decrease in movement and loss of appetite, which were probably attributable to surgical invasion. Eight animals died in this study. The causes of death were aspiration and pneumonia in 1 animal, aspiration in 2 animals, hoof disease in 1 animal, aspiration, pneumonia, and paralysis of the hindlimbs in 1 animal, and paralysis of the hindlimbs in 3 animals. All cases of paralysis of the hindlimbs occurred in animals that received 2 stent grafts. The stent grafts blocked a wide area of the branch vessels to the spinal cord, resulting in spinal cord ischemic paralysis. More than half of animals receiving 2 stent grafts survived in a good health condition, suggesting that the vascularity depends on individual animals even if they are the same species. The applicant explained that it is impossible to estimate the incidence of spinal cord ischemic paralysis in humans based on this result because sheep and humans have a totally different anatomy, including the vascularity.

The applicant explained that the incidence of spinal cord ischemic paralysis in humans cannot be estimated from the findings of hindlimb paralysis in 4 sheep in the performance study, because of anatomical differences between sheep and humans. PMDA therefore asked the applicant to explain reasons for selecting sheep as the test animals.

The applicant's response:

Sheep was selected as the test animal species for the study because it has the attributes listed below. Because of these attributes, the study can use test devices most similar to the clinical ones according to the recommended procedures for clinical use. Specifically, the study can use test devices of the same size as those for humans without reduction in size, to assess stent graft migration after long-term implantation following endovascular stent graft repair:

- The aorta is ≥20 mm in diameter.
- Pull-through can be made between the femoral artery and left common carotid artery, to secure an access route.
- Growth causes only minimal changes to the vessel diameter.
- Body weight and shape do not change significantly during a 1-year period (easy to control body weight).

As a result, [redacted].

PMDA's view:

Because fenestrated Najuta Stent Graft can be placed in the ascending aorta, the device may have an increased risk of cerebral infarction resulting from (a) the migration of atheroma fragments from the aortic arch during manipulation of the device, (b) blockage of blood flow to the brachiocephalic artery and common carotid artery, and (c) thrombosis caused by the exposed metal part of the stent skeleton contacting the branch vessels at the aortic arch.

PMDA asked the applicant to explain why fenestrated stent grafts were not evaluated in animal studies.

The applicant's explanation:

The risk for thrombosis with Najuta Stent Graft was assessed through histology using sections made of blood vessels implanted with Najuta Stent Graft together with the stent grafts. Histology showed no thrombus formation on the stent skeleton. Neither thrombus around the stent graft nor neointimal

formation on the inner surface of the stent graft was found throughout the entire assessment period. Najuta Stent Graft is a stent graft with a so-called endoskeleton, in which a graft is fixed to the outer surface of a Z stent skeleton with a suture. The Z stent skeleton is always exposed to the blood. Thrombus is more likely to be formed in a gap between the Z stent skeleton and graft, where blood flow is inhibited due to crease of graft, rather than the areas around fenestrations, which are closer to the heart and have a faster blood flow. For this reason, the risk of thrombosis associated with fenestrated stent grafts, as well as unfenestrated ones, can be assessed based on the results of the animal study using unfenestrated stent grafts. Najuta Stent Graft is associated with a low risk of thrombosis even at fenestrations of the stent grafts placed in the aorta. Migration of atheroma, etc. associated with device manipulation could not be quantitatively assessed, for the following reasons: (a) the animal study could not fully evaluate the migration of atheroma etc. because it used models not ideal for such evaluation, namely young and healthy sheep without any atheroma in the inner wall of the aorta or mural thrombosis; (b) a blood vessel model with an atheroma or mural thrombosis could not be created. The results of the clinical trial, etc. have shown that Najuta Stent Graft can be delivered safely to a destination in the ascending aorta. However, placement of Najuta Stent Graft in the ascending aorta may increase the risk for cerebral infarction due to migration of mural thrombosis or atheroma. Accordingly, the following precautionary statement is included in the package insert as a risk reduction strategy: “Najuta Stent Graft should not be used in patients with severe calcification, or mural thrombosis or atheroma around the area where the stent graft is to be placed.”

PMDA’s view:

Another animal study may be required to assess maneuverability, stent graft durability, migration resistance, and tissue reaction after placement. These attributes were, however, evaluated in the submitted study. Four sheep implanted with Najuta Stent Graft had paralysis of the hindlimbs, but the applicant explained that the incidence of spinal cord ischemic paralysis in humans cannot be estimated from the results in sheep because sheep and humans have a totally different anatomy, including the vascularity; this explanation is acceptable. The risk of spinal cord ischemic paralysis in humans using Najuta Stent Graft should be assessed based not only on animal studies but also on a clinical trial. The risk of thrombosis or cerebral infarction in humans using Najuta Stent Graft cannot be evaluated based on nonclinical studies using a vessel model or sheep, because of difficulty in creating an aneurysm model, anatomical differences between sheep and humans, etc. The risk for cerebral infarction in humans should be discussed based on the results of a clinical trial [see Section “8. Clinical data”].

5.(3) Study supporting the usage of the device

In order to evaluate the maneuverability during placement of Najuta Stent Graft, 1 or 2 stent grafts that were slightly curved, strongly curved, or connected were implanted in the aorta of 24 Suffolk sheep (18 females, 6 males). Of 24 animals, 23 were used also in study supporting the performance of the device.

In the study supporting the usage of the device, 2 models (shapes) of delivery sheaths were used depending on the implantation site and the stent graft models: the strongly curved model (U shape) and the least curved model (A shape). The sheaths had 3 different widths: the widest model (23 Fr), the narrowest model (21 Fr), and the special model for this study ([redacted]).

The test stent grafts were evaluated and observed for the easiness of device preparation for use, insertability of the stent graft set, pushability, trackability, and flexibility of the stent graft set, deployment completeness, release resistance, radiopacity of the stent graft, retracting of the delivery sheath, condition of the delivery sheath after placement, and hemostatic capability of the stent graft set. All of the models showed a satisfactory maneuverability.

PMDA's view:
Although no animal study investigated whether fenestrated stent grafts can be appropriately implanted at the desired site, the basic maneuverability of Najuta Stent Graft during implantation has been demonstrated, without any finding that precludes the use in humans.

6. Risk analysis

The applicant submitted documents summarizing the risk management system and its implementation status in reference to ISO 14971 "Medical devices - Application of risk management to medical devices."

PMDA reviewed and accepted the risk analysis data.

7. Manufacturing process

The applicant submitted information regarding the manufacturing process: data on the manufacturing process, manufacturing facilities, sterilization method (ethylene oxide gas sterilization), and quality control.

PMDA reviewed and accepted the manufacturing process.

8. Clinical data

The applicant submitted the results from a multicenter clinical trial conducted in Japan.

8.A. Outline of the clinical trial

8.A.(1) Multicenter clinical trial (trial period, [redacted] 20[redacted] to [redacted] 20[redacted])

8.A.(1).1) Methodology

A multicenter, open-label trial was conducted at 11 study sites in Japan, to evaluate the efficacy and safety of Najuta Stent Graft in endovascular repair of distal aortic arch aneurysm and thoracic

descending aortic aneurysm in comparison with open surgery. According to the inclusion and exclusion criteria listed below, historical controls were collected from patients registered in the Japan Adult Cardiovascular Surgery Database (JACVSD) who underwent open surgery (blood vessel prosthesis implantation) or endovascular stent graft repair (percutaneous endovascular stent graft repair) to treat true or false aneurysms of the distal aortic arch or descending aorta between [redacted], 20[redacted] and [redacted], 20[redacted] at any of the study sites participating in the trial. Data on historical controls undergoing stent graft repair were used as supplementary data because this treatment is widely used.

Patients meeting at least 1 of the following 3 inclusion criteria were included in the clinical trial group (i.e., the population receiving Najuta Stent Graft). Patients meeting criteria (a) and (c) were included in historical controls.

(a) Aortic aneurysm ≥50 mm in diameter.
(b) The aortic aneurysm has been enlarged by ≥5 mm per year.
(c) Cystic aortic aneurysm whose enlarged part is ≥10 mm larger than the normal blood vessel.

Patients meeting any of the following 4 anatomical exclusion criteria were excluded from the clinical trial group. Patients meeting any of the exclusion criteria (a), (c), and (d) were excluded from historical controls.

(a) The length of sealing zone between the bifurcation of the left common carotid artery and the aortic aneurysm is <20 mm.
(b) In patients whose left subclavian artery is not covered, the length of sealing zone between the bifurcation of the left common carotid artery and the aortic aneurysm is <20 mm.
(c) The length of sealing zone between the bifurcation of the celiac artery and the aortic aneurysm is <20 mm.
(d) The blood vessel at the sealing zones is <20 mm or ≥38 mm in diameter.

Of 127 patients enrolled in the trial, 117 were treated with Najuta Stent Graft (the clinical trial group) and included in Full Analysis Set (FAS) for efficacy analysis and in Safety Population (SP) for safety analysis. Per Protocol Set (PPS) included 111 patients, excluding 6 patients who did not complete the protocol-specified evaluation period for the primary endpoint due to death or study withdrawal. Historical controls included 256 patients (92 undergoing open surgery [the open surgery group]; 164 undergoing endovascular repair with an unapproved stent graft [the conventional repair group]) whose data were extracted from the JACVSD. The 256 patients were included in the FAS and SP. PPS included 211 patients (78 in the open surgery group, 133 in the conventional repair group), excluding 45 patients who were considered to have significant protocol violation or deviation, or have no evaluable primary endpoint data, according to the protocol for the clinical trial group.

Table 1 shows patient characteristics and vascular properties in the clinical trial group, the open surgery group, and the conventional repair group.

Table 1. Patient characteristics and vascular properties (PPS)

Characteristics		Clinical trial (Najuta Stent Graft) (N = 111)	Open surgery (N = 78)	Conventional repair (N = 211)
Age		72.9 ± 7.12*	69.9 ± 9.47	71.2 ± 8.21
Height (cm)		161.3 ± 8.20	160.5 ± 9.16	160.9 ± 8.28
Weight (kg)		61.7 ± 11.61	61.5 ± 10.37	62.8 ± 11.17
Sex	Male	91 (82.0%)	61 (78.2%)	172 (81.5%)
	Female	20 (18.0%)	17 (21.8%)	39 (18.5%)
Site of aortic aneurysm	Distal arch	74 (66.7%)	54 (69.2%)	124 (58.8%)
	Descending	37 (33.3%)	24 (30.8%)	87 (41.2%)
Shape of aortic aneurysm	Spindle-shaped	28 (25.2%)	34 (43.6%)	74 (35.1%)
	Cystic	83 (74.8%)	44 (56.4%)	137 (64.9%)
Previous aortic aneurysm diameter expansion	≥5 mm/year	75 (67.6%)	8 (10.3%)	13 (6.2%)
	<5 mm/year	18 (16.2%)	4 (5.1%)	6 (2.8%)
	Unknown	18 (16.2%)	66 (84.6%)	192 (91.0%)

*, Mean ± standard deviation

The primary endpoint was "survival rate at 12 months after aneurysm-related treatment." Aneurysm treatment-related deaths were defined as "deaths from aneurysm rupture, haemorrhage, vascular injury, dissociation, occlusion, infection, thrombosis, or pressure on adjacent organs." The following secondary endpoints were also selected: Technical success rate, early success rate, and treatment success rate for efficacy evaluation; the incidence of major complications and survival rate at 12 months postoperative for safety evaluation; and operation time, length of ICU stay, start time of oral ingestion, and duration of hospitalization for clinical usefulness evaluation. In addition to these endpoints, the condition of the implanted stent graft (migration and damage) and a change in aortic aneurysm diameter were also investigated. Technical success, early success, treatment success, and major complications were defined as below.

Technical success:

The thoracic aorta stent graft is delivered and implanted at the desired site, with a graft patency after implantation as confirmed by perioperative angiography and the delivery sheath is removed without any problem.

Early success:

Technical success is achieved, with no Type I, Type III, or Type IV endoleak,[3] no acute procedural adverse event, and no major complication, with favorable graft patency as confirmed by CT scan,

[3] Type I: A leak due to incomplete seal between a stent graft and a host aorta.
Type III: A leak through an overlapping segment between stent grafts or a leak due to damage to a stent graft.
Type IV: A leak due to the porosity of a stent graft.
Type II (not included in the above definition): A leak associated with the back flow from the side branches of the aortic aneurysm.

angiography, or Duplex ultrasound (performed only in patients with contraindications to contrast-enhanced CT because of renal failure, etc.) at hospital discharge (within 30 days postoperative).

Treatment success:
Technical success is achieved, with no Type I, Type III, or Type IV endoleak at 12 months postoperative, no major complication, and no ≥5 mm expansion of the aneurysm, with favorable graft patency as confirmed by CT scan, angiography, or Duplex ultrasound (performed only in patients with contraindications to contrast-enhanced CT because of renal failure, etc.) throughout the entire evaluation period.

Major complications: Events such as heart disorders requiring surgical treatment, long-term mechanical ventilation requiring tracheostomy, renal diseases newly requiring hemodialysis, aortic fistula, pressure on adjacent organs, mesenteric ischaemia (blood flow disturbance in the entire or part of the small or large intestine), paraplegia or paraparesis lasting for ≥30 days postoperative, pulmonary embolism, cerebral infarction, cerebral haemorrhage, multi-organ failure, ischemia of lower extremities, aneurysm rupture, and vascular disorders (vascular injury and aortic dissection).

The applicant conducted a between-group comparison (Najuta Stent Graft vs. open surgery) of efficacy and safety, adjusted for patient characteristics, by matching historical controls in the open surgery group (PPS for efficacy analysis and SP for safety analysis) to patients in the clinical trial group at a ratio of 1:1 using a propensity score for study site, location of aortic aneurysm, and eligibility for stent graft repair or open surgery.

The following 2 types of matching were conducted using the calculated propensity scores:
(a) A historical control in the open surgery group who best matches each patient in the clinical trial group is selected without restricting a propensity score range (the unrestricted matched population).
(b) A historical control in the open surgery group who matches each patient in the clinical trial group with a propensity score difference of not more than [redacted] is selected (the restricted matched population).

Historical controls in the conventional repair group were also matched to each patient in the clinical trial group in the same manner for efficacy and safety analysis. Table 2 shows the name of each analysis population after matching.

Table 2. Analysis populations after matching

Analysis population	Matched treatment	Matching category	Population name	No. of patients
Efficacy analysis population (PPS)	Open surgery	Unrestricted matching	Clinical trial PPS population matched (unrestricted) to open surgery PPS population	48
			Open surgery PPS population matched (unrestricted) to clinical trial PPS population	48
		Restricted matching	Clinical trial PPS population matched (restricted) to open surgery PPS population	31
			Open surgery PPS population matched (restricted) to clinical trial PPS population	31
	Conventional repair	Unrestricted matching	Clinical trial PPS population matched (unrestricted) to conventional repair PPS population	89
			Conventional repair PPS population matched (unrestricted) to clinical trial PPS population	89
		Restricted matching	Clinical trial PPS population matched (restricted) to conventional repair PPS population	55
			Conventional repair PPS population matched (restricted) to clinical trial PPS population	55
Safety analysis population (SP)	Open surgery	Unrestricted matching	Clinical trial SP population matched (unrestricted) to open surgery SP population	53
			Open surgery SP population matched (unrestricted) to clinical trial SP population	53
		Restricted matching	Clinical trial SP population matched (restricted) to open surgery SP population	34
			Open surgery SP population matched (restricted) to clinical trial SP population	34
	Conventional repair	Unrestricted matching	Clinical trial SP population matched (unrestricted) to conventional repair SP population	98
			Conventional repair SP population matched (unrestricted) to clinical trial SP population	98
		Restricted matching	Clinical trial SP population matched (restricted) to conventional repair SP population	63
			Conventional repair SP population matched (restricted) to clinical trial SP population	63

The efficacy analysis was intended to demonstrate the non-inferiority of Najuta Stent Graft to open surgery in survival rate after aneurysm-related treatment. Najuta Stent Graft is considered non-inferior in efficacy to open surgery if the lower limit of 95% confidence interval (CI) of survival rate difference (between Najuta Stent Graft and open surgery) at 12 months after aneurysm-related treatment exceeds −10%. Najuta Stent Graft is considered superior in safety to open surgery if the upper limit of 95% CI of treatment difference (between Najuta Stent Graft and open surgery) in the incidence of major complications, is ≤0%.

In the clinical trial, 117 subjects received 176 stent grafts of 43 models (out of 64 models available). The 176 stent grafts (including 79 stent grafts of 7 fenestrated models) consisted of 125 straight ones and 51 tapered ones. Each subject received 1 to 3 stent grafts. Many patients received 1 stent graft (65 of 117 subjects [55.6%]), followed by 2 stent grafts (45 of 117 subjects [38.5%]), and 3 stent grafts (7 of 117 subjects [6.0%]). The most common implant location was Zone 0 (66 of 176 stent grafts [37.5%]), followed by Zone 4 (48 of 176 stent grafts [27.3%]) (Table 3 and Figure 4).

Table 3. Implant location of stent graft (FAS)

Implant location (Zone category)	Number of stent grafts (N = 176)	Number of subjects (N = 117)
Zone 0	37.5% (66/176)	56.4% (66/117)
Zone 1	3.4% (6/176)	5.1% (6/117)
Zone 2	10.8% (19/176)	4.3% (5/117)
Zone 3	21.0% (37/176)	21.4% (25/117)
Zone 4	27.3% (48/176)	12.8% (15/117)

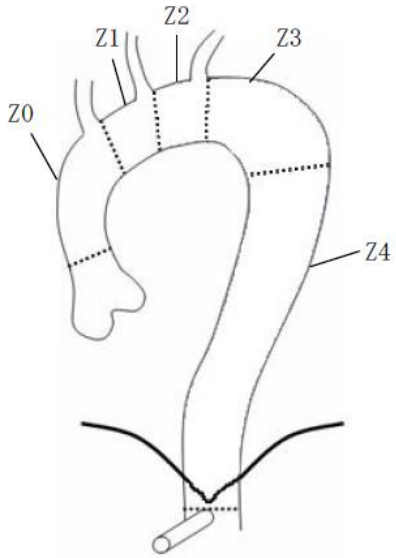


Figure 4. Zone category

8.A.(1).2) Trial results

Table 4 shows the results of survival rates at 12 months after aneurysm-related treatment, the primary efficacy endpoint. The applicant did not calculate 95% CI (%) of treatment difference (between Najuta Stent Graft and open surgery) in survival rate at 12 months for the matched (both restricted and unrestricted) PPS populations, because no aneurysm-related death occurred in matched patients in the clinical trial group. Nevertheless, in the matched (unrestricted) PPS populations, Najuta Stent Graft was considered non-inferior to open surgery, according to (a) treatment difference in the survival rate and (b) individual 95% CI values of the survival rate with both treatments. Also in the matched (restricted) PPS populations, Najuta Stent Graft was considered non-inferior to open surgery, although 95% CI of treatment difference in the survival rate was not calculated because of the absence of death in both treatment groups. In the unmatched populations, treatment difference (between Najuta Stent Graft and open surgery) in the survival rate at 12 months after aneurysm-related treatment was 1.1% (95% CI, −4.1%, 6.4%); the lower limit of the 95% CI thus exceeded −10%, showing the non-inferiority of Najuta Stent Graft to open surgery.

In the matched populations for conventional repair, treatment difference (between Najuta Stent Graft and open surgery) in the survival rate at 12 months after aneurysm-related treatment was as follows:

The matched (unrestricted) populations: −1.2% (95% CI, −6.0%, 3.7%).

The matched (restricted) populations: 0.0% (95% CI, −5.0%, 5.0%).

Table 4. Summery statistics of survival rate at 12 months after aneurysm-related treatment (PPS)

Analysis population		Days to aneurysm-related death		Survival rate at 12 months postoperative (2-sided 95% CI [%])	Treatment difference in survival rate at 12 months postoperative (95% CI [%])
Matched (unrestricted) PPS population	Clinical trial (Najuta Stent Graft) (N = 48)	No. of deaths	0	100.0 (92.6, 100.0)	4.2
		Median	-		
		Min-Max	-		
	Open surgery (N = 48)	No. of deaths	2	95.8 (86.0, 98.8)	
		Median	21		
		Min-Max	12-29		
Matched (restricted) PPS population	Clinical trial (Najuta Stent Graft) (N = 31)	No. of deaths	0	100.0 (89.0, 100.0)	0.0
		Median	-		
		Min-Max	-		
	One surgery (N = 31)	No. of deaths	0	100.0 (89.0, 100.0)	
		Median	-		
		Min-Max	-		
Unmatched population	Clinical trial (Najuta Stent Graft) (N = 111)	No. of deaths	3	97.3 (92.4, 99.1)	1.1 (−4.1, 6.4)
		Median	145		
		Min-Max	22-251		
	Open surgery (N = 78)	No. of deaths	3	96.2 (89.3, 98.7)	
		Median	29		
		Min-Max	12-69		

The percentage of "technical success," "early success," and "treatment success," which were secondary efficacy endpoints, were 99.1% (116 of 117 subjects), 78.9% (92 of 117 subjects), and 63.2% (74 of 117 subjects), respectively (Tables 5 to 7).

Table 5. Technical success rate (FAS)

Evaluation of technical success	FAS (N = 117)	
	Number of subjects	%
Success	116	99.1
Failure	1	0.9
Failure in terms of implant location	1	0.9

Table 6. Early success rate (FAS)

Evaluation of early success	FAS (N = 117)	
	Number of subjects	%
Success	92	78.6
Failure	24	20.5
Technical failure	1	0.9
Endoleak[*1] confirmed by postoperative CT	7	6.0
Acute operation-related adverse event	1	0.9
Major complication	15	12.8
Paraplegia or paraparesis lasting for ≥30 days postoperative	2	1.7
Cerebral infarction	7	6.0
Vascular injury	6	5.1
No graft patency confirmed	0	0.0
Unevaluable	1	0.9

[*1] Type I, Type III, Type IV

Table 7. Treatment success rate (FAS)

Evaluation of treatment success	FAS (N = 117)	
	Number of subjects	%
Success	74	63.2
Failure	33	28.2
Technical failure	1	0.9
Endoleak[*1] confirmed by CT at 12 months postoperative	5	4.3
Major complications	26	22.2
Long-term mechanical ventilation requiring tracheostomy	2	1.7
Renal disease newly requiring hemodialysis	2	1.7
Paraplegia or paraparesis lasting for ≥30 days postoperative	3	2.6
Pulmonary embolism	1	0.9
Cerebral infarction	7	6.0
Cerebral haemorrhage	4	3.4
Vascular injury (vascular injury and aortic dissection)	7	6.0
No graft patency confirmed	0	0.0
Aortic aneurysm diameter expansion[*2]	7	6.0
Unevaluable	10	8.5
Death before Month 12	3	2.6
No follow-up at Month 12 because of withdrawal, dropout, etc.	3	2.6
Endoleak not assessed because of switching to plain CT	4	3.4

[*1] Type I, Type III, Type IV [*2] ≥5 mm after operation.
Subjects with treatment failure for multiple reasons were included in the calculation for each reason.

The incidence of adverse events in the clinical trial group was 99.1% (116 of 117 subjects) between operation and 12 months postoperative (the entire evaluation period). The following are the incidences of adverse events by evaluation points:

- 99.1% (116 of 117 subjects) up to hospital discharge
- 47.0% (55 of 117 subjects) between hospital discharge and 3 months postoperative
- 34.2% (40 of 117 subjects) between 3 and 6 months postoperative
- 35.9% (42 of 117 subjects) between 6 and 12 months postoperative

Table 8 shows adverse events with an incidence of ≥10% over the entire evaluation period.

Table 8. Incidence of adverse events (SP) and malfunctions (FAS)
(Incidence, ≥10% over the entire evaluation period)

	Entire evaluation period		Between operation and hospital discharge		Between hospital discharge and 3 months postoperative		Between 3 and 6 months postoperative		Between 6 and 12 months postoperative	
Subjects included in analysis	117		117		117		117		117	
	Adverse event	Malfunction	Adverse event	Malfunction	Adverse event	Malfunction	Adverse event	Malfunction	Adverse event	Malfunction
Total	116 (99.1%)	94 (80.3%)	116 (99.1%)	92 (78.6%)	55 (47.0%)	13 (11.1%)	40 (34.2%)	5 (4.3%)	42 (35.9%)	12 (10.3%)
Postoperative pyrexia	104 (88.9%)	75 (64.1%)	103 (88.0%)	75 (64.1%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
C-reactive protein increased	85 (72.6%)	61 (52.1%)	82 (70.1%)	60 (51.3%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	2 (1.7%)	1 (0.9%)
Fibrin degradation products increased	61 (52.1%)	49 (41.9%)	58 (49.6%)	48 (41.0%)	2 (1.7%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Wound complication	55 (47.0%)	0 (0.0%)	49 (41.9%)	0 (0.0%)	5 (4.3%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood fibrinogen increased	51 (43.6%)	38 (32.5%)	51 (43.6%)	38 (32.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Back pain	38 (32.5%)	1 (0.9%)	28 (23.9%)	1 (0.9%)	5 (4.3%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	4 (3.4%)	0 (0.0%)
Insomnia	36 (30.8%)	0 (0.0%)	30 (25.6%)	0 (0.0%)	4 (3.4%)	0 (0.0%)	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Constipation	30 (25.6%)	0 (0.0%)	27 (23.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Nausea	26 (22.2%)	1 (0.9%)	25 (21.4%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Headache	24 (20.5%)	3 (2.6%)	19 (16.2%)	2 (1.7%)	1 (0.9%)	1 (0.9%)	3 (2.6%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Blood pressure increased	24 (20.5%)	1 (0.9%)	23 (19.7%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypoaesthesia	23 (19.7%)	6 (5.1%)	18 (15.4%)	5 (4.3%)	3 (2.6%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Vomiting	23 (19.7%)	2 (1.7%)	18 (15.4%)	2 (1.7%)	2 (1.7%)	0 (0.0%)	2 (1.7%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Chills	21 (17.9%)	11 (9.4%)	19 (16.2%)	11 (9.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)	0 (0.0%)
Haemoglobin decreased	20 (17.1%)	2 (1.7%)	18 (15.4%)	2 (1.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Gait disturbance	20 (17.1%)	1 (0.9%)	17 (14.5%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Platelet count decreased	16 (13.7%)	8 (6.8%)	12 (10.3%)	7 (6.0%)	2 (1.7%)	0 (0.0%)	2 (1.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Haematocrit decreased	16 (13.7%)	2 (1.7%)	14 (12.0%)	2 (1.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Red blood cell count decreased	16 (13.7%)	2 (1.7%)	16 (13.7%)	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Puncture site pain	16 (13.7%)	0 (0.0%)	16 (13.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Malaise	14 (12.0%)	4 (3.4%)	9 (7.7%)	4 (3.4%)	2 (1.7%)	0 (0.0%)	2 (1.7%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Decreased appetite	14 (12.0%)	1 (0.9%)	10 (8.5%)	1 (0.9%)	2 (1.7%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Hypertension	14 (12.0%)	0 (0.0%)	7 (6.0%)	0 (0.0%)	2 (1.7%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	4 (3.4%)	0 (0.0%)
Post procedural haemorrhage	13 (11.1%)	0 (0.0%)	12 (10.3%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stent-graft endoleak	12 (10.3%)	11 (9.4%)	7 (6.0%)	6 (5.1%)	4 (3.4%)	4 (3.4%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Aortic aneurysm	12 (10.3%)	9 (7.7%)	0 (0.0%)	0 (0.0%)	2 (1.7%)	0 (0.0%)	2 (1.7%)	2 (1.7%)	8 (6.8%)	7 (6.0%)

The incidence of serious adverse events was 37.6% (44 of 117 subjects) over the entire evaluation period: 14.5% (17 of 117 subjects) at hospital discharge, 11.1% (13 of 117 subjects) between hospital discharge and 3 months postoperative, 11.1% (13 of 117 subjects) between 3 and 6 months postoperative,

and 10.3% (12 of 117 subjects) between 6 and 12 months postoperative. Table 9 shows serious adverse events reported by ≥2 subjects over the entire evaluation period. Aortic aneurysm diameter expansion persisted in 1 subject. The other subjects recovered or were recovering, except for 1 subject with unknown outcome.

Table 9. Incidence of serious adverse events (SP) and malfunctions (FAS)
(serious adverse events reported by ≥2 subjects over the entire evaluation period)

	Entire evaluation period		Between operation and hospital discharge		Between hospital discharge and 3 months postoperative		Between 3 and 6 months postoperative		Between 6 and 12 months postoperative	
Subjects included in analysis	117		117		117		117		117	
	Adverse event	Malfunction	Adverse event	Malfunction	Adverse event	Malfunction	Adverse event	Malfunction	Adverse event	Malfunction
Total	44 (37.6%)	17 (14.5%)	17 (14.5%)	12 (10.3%)	13 (11.1%)	3 (2.6%)	13 (11.1%)	1 (0.9%)	12 (10.3%)	4 (3.4%)
Cerebral infarction	6 (5.1%)	6 (5.1%)	6 (5.1%)	6 (5.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Aortic aneurysm	4 (3.4%)	2 (1.7%)	0 (0.0%)	0 (0.0%)	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)	2 (1.7%)
Cerebral haemorrhage	4 (3.4%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	2 (1.7%)	0 (0.0%)
Stent-graft endoleak	2 (1.7%)	2 (1.7%)	2 (1.7%)	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pneumonia	2 (1.7%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Muscular weakness	2 (1.7%)	1 (0.9%)	2 (1.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac failure	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Renal failure chronic	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Haematochezia	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Deaths occurred in 5 patients (4.3%) over the entire evaluation period: 1 patient (0.9%) at hospital discharge, 1 patient (0.9%) at 3 months postoperative, 1 patient (0.9%) at 6 months postoperative, and 2 patients (1.7%) at 12 months postoperative. The first death occurred 22 days after implantation of Najuta Stent Graft. This subject also experienced haemorrhage due to right femoral arterial rupture during treatment of MRSA infection of a wound at the right inguinal region. Although haemorrhage was stopped, the subject had cardio-respiratory arrest 3 days later. The subject also had massive gastrointestinal haemorrhage and a pathological diagnosis of coronary artery arteriosclerosis, suggesting that acute circulatory failure caused myocardial ischemia, resulting in death. The death was therefore considered unrelated to Najuta Stent Graft. The second death occurred 111 days after implantation of Najuta Stent Graft. The death was considered unrelated to Najuta Stent Graft, because it was probably caused by massive haemorrhage during laparoscopic cholecystectomy and by loss and failure of blood coagulating and hemostatic ability due to prolonged shock state. The third death occurred 145 days after implantation of Najuta Stent Graft. The subject was found dead at home. Autopsy confirmed cardiac death. The death was considered unrelated to Najuta Stent Graft, because CT scan at 3-month visit had revealed no abnormalities, including endoleaks. The fourth death occurred 272 days after implantation of Najuta Stent Graft. The death was considered unrelated to Najuta Stent Graft, because it was due to

interstitial pneumonia (a serious complication) that had been persisting since the start of trial. The fifth death, occurring 410 days after implantation of Najuta Stent Graft, was due to sepsis. The subject experienced complete paraplegia after implantation and was transferred to another hospital for rehabilitation. At the hospital, the subject had respiratory failure and acute renal failure. The aggravated systemic condition appeared to have led to aggravation of pressure sore. The causal relationship of the death to Najuta Stent Graft could not be ruled out.

The incidence of major complications is presented in Table 10. In the matched (unrestricted) SP populations, treatment difference (between Najuta Stent Graft and open surgery) in the incidence of major complications was −13.1% (95% CI, −26.3%, −0.3%). The upper limit of 95% CI was ≤0%, showing the superiority of Najuta Stent Graft to open surgery. In the matched (restricted) SP populations, however, Najuta Stent Graft was not superior to open surgery.

Table 10. Summery statistics of the incidence of major complications (SP)

Analysis population		Incidence of major complications (95% CI, %)	Treatment difference (95% CI, %)
Matched (unrestricted) SP population	Clinical trial (Najuta Stent Graft) (N = 53)	7.5 (2.9, 17.8)	−13.3 (−26.3, −0.3)
	Open surgery (N = 53)	20.8 (12.0, 33.5)	
Matched (restricted) SP population	Clinical trial (Najuta Stent Graft) (N = 34)	5.9 (1.6, 19.1)	−5.9 (−19.3, 7.5)
	Open surgery (N = 34)	11.8 (4.7, 26.7)	

The incidence of major complications in the clinical trial group (unmatched population) was 19.7% (23 of 117 subjects). Three subjects experienced ≥2 major complications. A total of 27 major complications occurred. Common major complications (incidence, ≥2%) were cerebral infarction and vascular injury (6.0% [7 of 117 subjects] each for iliac artery injury, femoral artery injury, and vascular injury), cerebral haemorrhage (3.4%, 4 of 117 subjects), and paraplegia or paraparesis lasting for ≥30 days postoperative (2.6%, 3 of 117 subjects). The open surgery group (unmatched population) had 19 major complications. Common major complications (incidence, ≥2%) were cerebral infarction (6.5%, 6 of 92 subjects), long-term mechanical ventilation requiring tracheostomy (4.3%, 4 of 92 subjects), multi-organ failure (3.3%, 3 of 92 subjects), and renal diseases newly requiring hemodialysis, paraplegia or paraparesis lasting for ≥30 days postoperative, and vascular disorders (2.2%, 2 of 92 subjects for each event).

Images taken between 0 and 12 months postoperative were analyzed at the core laboratory. The incidence of changes in aortic aneurysms and endoleaks is presented in Table 11. Subjects were classified as “unevaluable” if they had not undergone diagnostic imaging because of withdrawal, dropout, death, etc. At all evaluation points, graft patency was maintained in all subjects. Neither stent

graft migration (antegrade or retrograde migration of ≥10 mm from the location shown on the image taken at hospital discharge after surgery) nor deformity (damage) was detected.

During operation, stent graft migration occurred in 3 of 117 subjects (2.6%). The first case of stent graft migration occurred during vessel wall apposition of a deployed stent graft by the expanded balloon attached to the catheter. During the apposition, blood flow pushed the balloon toward the distal side, resulting in Type I endoleak. An additional stent graft was implanted during operation to treat the endoleak. The second case occurred in a subject who received 2 stent grafts. While the delivery sheath was retracted, it was caught by the skeleton of a stent graft, moving the stent graft toward the distal side. This resulted in an insufficient overlap between the stent grafts, causing Type III endoleak at the overlapping segment. An additional stent graft was implanted to treat the endoleak. The third case occurred during vessel wall apposition of a deployed stent graft by the expanded balloon attached to the catheter. During the apposition, blood flow pushed the balloon, moving the stent graft toward the distal side. As a result, the stent graft covered the celiac artery, posing a risk of ischemia; a stent was implanted in the celiac artery to prevent ischemia.

Table 11. Changes in aortic aneurysms and endoleaks between 0 and 12 months postoperative

Characteristic		Between operation and hospital discharge	3 months postoperative	6 months postoperative	12 months postoperative
Change in aortic aneurysm N = 117	No	-	100 (85.5%)	83 (70.9%)	63 (53.8%)
	Yes	-	10 (8.5%)	25 (21.4%)	42 (35.9%)
	Enlarged	-	0 (0.0%)	2 (1.7%)	7 (6.0%)
	Shrunk	-	10 (8.5%)	23 (19.7%)	35 (29.9%)
	Unevaluable	-	7 (6.0%)	9 (7.7%)	12 (10.3%)
Endoleak N = 117	No	101 (86.3%)	93 (79.5%)	85 (72.6%)	87 (74.4%)
	Yes	13 (11.1%)	13 (11.1%)	11 (9.4%)	11 (9.4%)
	Type I	5 (4.3%)	5 (4.3%)	4 (3.4%)	3 (2.6%)
	Type II	6 (5.1%)	7 (6.0%)	7 (6.0%)	7 (6.0%)
	Unknown	2 (1.7%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
	Unevaluable*	3 (2.6%)	11 (9.4%)	21 (17.9%)	19 (16.2%)

* Endoleak status could not be evaluated.

8.B Outline of the review conducted by PMDA

PMDA reviewed the data submitted, focusing on the following points.

8.B.(1) Clinical positioning of Najuta Stent Graft

PMDA asked the applicant to explain the clinical advantage of fenestration(s), the structure characteristic of Najuta Stent Graft.

The applicant's explanation:

When an aneurysm extends into the lesser curvature of the distal aortic arch, conventional stent grafts cannot provide an enough sealing zone at the proximal side of the aneurysm. On the other hand, fenestrated Najuta Stent Graft can maintain blood flow in the branch vessels of the arch, while providing

an enough sealing zone at the proximal side of the lesser curvature, and blocking blood flow to the aneurysm (Figure 3). For this reason, Najuta Stent Graft is expected to expand the anatomical eligibility of aortic aneurysms for stent graft repair in clinical practice, compared with approved similar devices.

In the treatment of aortic aneurysms in the lesser curvature of the distal aortic arch, conventional thoracic stent grafts require a sealing zone of ≥20 mm from the side of the left common carotid artery, while Najuta Stent Graft can be used when a sealing zone of ≥20 mm from the left common carotid artery bifurcation is obtained (Figure 5). Aortic aneurysms commonly occur in the lesser curvature region of the distal aortic arch, and Najuta Stent Graft offers new option of stent graft repair for such aneurysms; this is of great clinical significance.

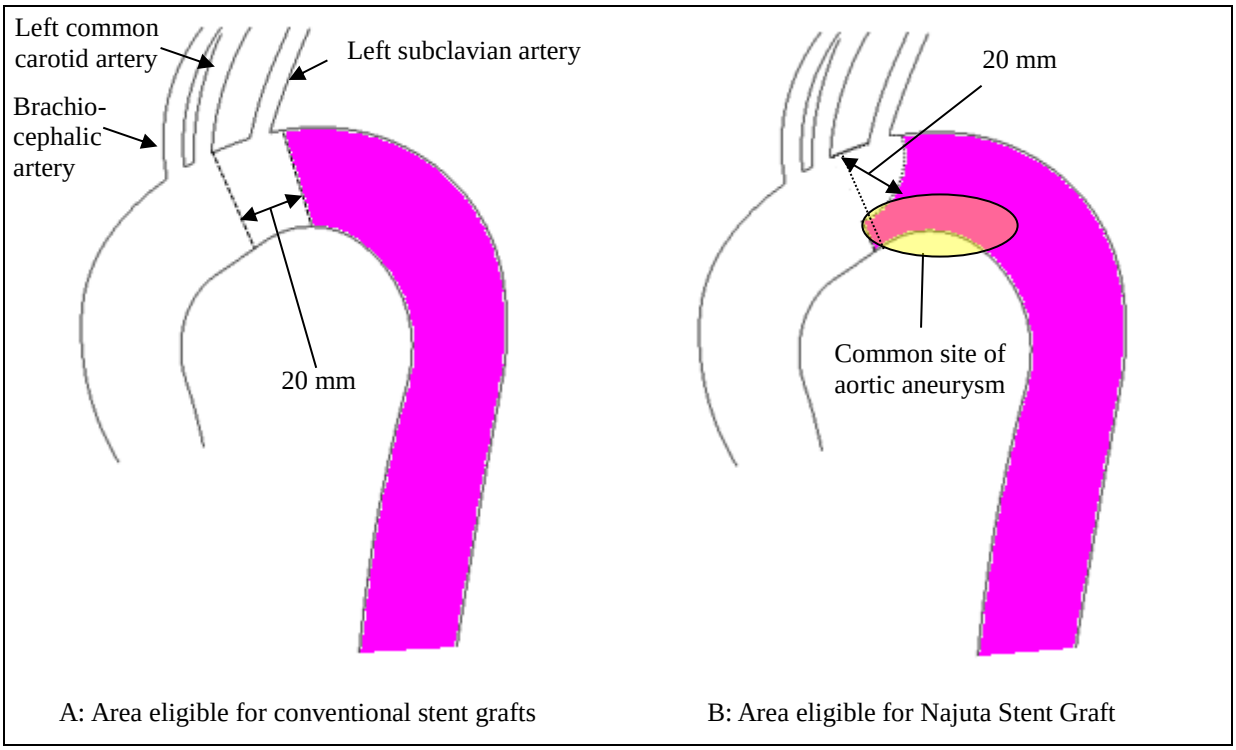


Figure 5. Application area of Najuta Stent Graft and conventional stent grafts

PMDA's view:

Currently, hybrid thoracic endovascular aortic repair (TEVAR) is indicated for the treatment of patients having no sealing zone of ≥20 mm from the lesser curvature side of the left common carotid artery in the lesser curvature area of the aortic arch, a common site of aortic aneurysms. Hybrid TEVAR is the combination of (a) aortic arch replacement or revascularization to secure blood flow to the head and neck and (b) thoracic endovascular aortic repair. Hybrid TEVAR is invasive, involving open surgery. Further, in some patients eligible for conventional stent graft repair, the stent graft cannot be attached tightly to the vessel wall because of the curve of the aortic arch, resulting in endoleaks. Najuta Stent Graft is a novel less-invasive medical device expected to treat aortic aneurysms that cannot be treated with conventional stent grafts alone.

8.B.(2) Appropriateness of trial design

8.B.(2).1) Control group

The applicant's explanation about appropriateness of the control group:

The applicant initially discussed the feasibility of a randomized controlled trial in order to prevent selection bias of patients, to evaluate Najuta Stent Graft both as a medical device and as a treatment. However, open surgery is highly invasive involving thoracotomy to expose the aorta, while endovascular repair requires only an incision in the inguinal region. The immediate postoperative condition would therefore differ significantly between the 2 treatments of thoracic aortic aneurysms. In addition, it is difficult to obtain patient consent for randomization to either of the 2 treatments that differ markedly in invasiveness. For these reasons, conducting a randomized controlled trial was very difficult. If an open-label, surgery-controlled trial were conducted, elderly patients and high-risk patients would be more likely to be assigned to endovascular repair. Imbalance of patient characteristics and risk factors between the Najuta Stent Graft group and the control group may cause a profound bias in evaluation. The applicant therefore considered a historical control design where historical control data (used as the control group in the clinical trial) are extracted from epidemiological data on the results of past open surgeries conducted on the initiative of the Japanese Society for Vascular Surgery. As a result, the clinical trial was designed to use epidemiological data as historical controls. The historical control data consist of results of open surgeries conducted before the advent of permanent stent graft implantation at the same medical institutions where trial patients receive Najuta Stent Graft. The trial was designed to minimize biases, including factors affecting the treatment outcome of aortic aneurysm (the indication of Najuta Stent Graft) and technical differences between study sites.

PMDA's view:

Najuta Stent Graft can treat aortic aneurysms ineligible for conventional thoracic stent grafts, because it offers fenestrated models. The standard treatment of such aneurysms is open surgery. This means that the efficacy and safety of Najuta Stent Graft should be evaluated in a randomized surgery-controlled trial. On the basis of the clinical situation in Japan, however, the applicant's explanation about the impracticability of a randomized controlled trial of Najuta Stent Graft is understandable. In addition, an open-label controlled trial would cause patient selection biases, and an uncontrolled trial would complicate the evaluation of trial results. The applicant therefore selected a historically controlled trial, by using data on open surgery conducted before the advent of permanent stent graft repair at the same medical institutions where trial patients receive Najuta Stent Graft, and by minimizing biases, including factors affecting the treatment outcome of aortic aneurysm (the indication of Najuta Stent Graft) and technical differences between study sites. This trial design, if used properly, is expected to provide a certain amount of data for comparing Najuta Stent Graft and open surgery. It is acceptable to collect historical controls from JACVSD-registered data on open surgeries conducted to treat true or false

aneurysm in the distal aortic arch or descending aorta between [redacted], 20[redacted] and [redacted], 20[redacted] at any of the study sites participating in the trial.

8.B.(2).2) Rationale for primary endpoint

The applicant's rationale for the primary endpoint (i.e., survival rate after aneurysm-related treatment):
The primary efficacy endpoint was defined as survival rate related only to aneurysm treatment, for the following reasons: (a) According to a literature search for open surgeries of thoracic aortic aneurysms conducted in Japan, most deaths associated with blood vessel prosthesis implantation to treat thoracic aortic aneurysms occurred at hospitals. (b) The clinical trial group would include high-risk patients with some risk factors that preclude open surgery.

PMDA's view:
In the clinical trial, "aneurysm treatment-related deaths" were defined as "deaths from aneurysm rupture, haemorrhage, vascular injury, dissociation, occlusion, infection, thrombosis, or pressure on adjacent organs." It is reasonable to evaluate the clinical usefulness of Najuta Stent Graft in the target patient population based on the primary endpoint of the "survival rate after aneurysm-related treatment." The evaluation period should be as long as practical because the aim of treatment is to cure aneurysm. As with patients treated with approved stent grafts, patients receiving Najuta Stent Graft should be evaluated for 12 months and followed up for 5 years after implantation.

8.B.(3) Efficacy

8.B.(3).1) Comparison with open surgery

The applicant's rationale for the non-inferiority margin of 10% for the primary endpoint of the trial:
There are no consensus on the non-inferiority margin for non-inferiority comparisons of thoracic aortic aneurysm treatments. Accordingly, the non-inferiority margin for the trial was selected based on the clinical field of antibiotics, because the efficacy rates of antibiotics (80% to 95%) are similar to those of thoracic aortic aneurysm treatments. Because an equivalence margin of 5% to 10% is usually used for the evaluation of antibiotics in both Japan and the US, the non-inferiority margin of 10% was used in the trial.

In the trial, the planned propensity matching analysis of PPS populations was intended to demonstrate the non-inferiority of Najuta Stent Graft to open surgery. However, the propensity matching analysis could not be performed successfully because the confidence interval for treatment difference could not be calculated due to the absence of aneurysm-related death in some populations. In addition, logistic analysis demonstrated no profound effects of risk factors due to propensity matching on the results. For these reasons, propensity matching appeared not to affect the results. The propensity matching analysis,

which reduces the sample size, was positioned as sensitivity analysis (secondary analysis) that helps interpretation of the trial results.

PMDA's view on the efficacy of Najuta Stent Graft:

The applicant selected the non-inferiority margin for the trial based on those used in another field because there were no consensus on the non-inferiority margin for a comparison of thoracic aortic aneurysm treatments; this applicant's strategy is not appropriate. The acceptable non-inferiority margin should have been established based also on the results of the clinical studies of approved stent grafts. In general, the position of primary or secondary analysis should not be changed after trial results become available. In the trial, the non-inferiority could not be assessed by the original primary analysis because no aneurysm-related death occurred in the matched patients who received Najuta Stent Graft and therefore 95% CI for treatment difference (between Najuta Stent Graft and open surgery) could not be calculated. However, the survival rates and its 95% CI in both treatment groups suggested the non-inferiority of Najuta Stent Graft to open surgery. In addition, the comparison in the unmatched population (although not positioned as the primary analysis) showed the non-inferiority of Najuta Stent Graft to open surgery according to the protocol-defined criteria, supporting the results in the matched populations. PMDA concludes that these results show the non-inferior efficacy of Najuta Stent Graft to open surgery.

8.B.(3).2) Results in patients ineligible for treatment with conventional thoracic stent grafts

Of subjects treated in the clinical trial, those with a proximal neck length of <20 mm were classified as "subjects ineligible for conventional thoracic stent grafts," while those with a proximal neck length of ≥20 mm were classified as "subjects eligible for conventional thoracic stent grafts." Table 12 shows results in subjects ineligible or eligible for conventional stent grafts.

PMDA's view

The safety and efficacy results were consistent regardless of whether subjects were eligible or ineligible for conventional stent grafts. Najuta Stent Graft is therefore expected to have similar efficacy and safety in the treatment of thoracic aortic aneurysm regardless of eligibility for conventional stent grafts.

Table 12. Mortality, technical success rate, and incidence of major complications in subjects ineligible or eligible for conventional stent grafts

		Ineligible for conventional stent grafts				Eligible for conventional stent grafts			
Number of subjects		54				63			
		≤30 days postoperative		>30 days and ≤12 months postoperative		≤30 days postoperative		>30 days and ≤12 months postoperative	
		No. of subjects	Incidence	No. of subjects	Incidence	No. of subjects	Incidence	No. of subjects	Incidence
Aneurysm-related death		1	1.9%	1	1.9%	0	0.0%	1	1.6%
All-cause death		1	1.9%	3	5.6%	0	0.0%	1	1.6%
Technical success		54	100%	-	-	62	98.4%	-	-
Major complications (total)		6	11.1%	2	3.7%	9	14.3%	9	14.3%
Heart disorder requiring surgical treatment		0	0.0%	0	0.0%	0	0.0%	0	0.0%
Long-term mechanical ventilation requiring tracheostomy		0	0.0%	1	1.9%	0	0.0%	1	1.6%
Renal disease newly requiring hemodialysis		0	0.0%	0	0.0%	0	0.0%	2	3.2%
Aortic fistula		0	0.0%	0	0.0%	0	0.0%	0	0.0%
Pressure on adjacent organs		0	0.0%	0	0.0%	0	0.0%	0	0.0%
Mesenteric ischemia		0	0.0%	0	0.0%	0	0.0%	0	0.0%
Paraplegia or paraparesis lasting for ≥30 days postoperative		1	1.9%	0	0.0%	1	1.6%	1	1.6%
Pulmonary embolism		0	0.0%	0	0.0%	0	0.0%	1	1.6%
Cerebrovascular disease	Cerebral infarction	4	7.4%	0	0.0%	3	4.8%	0	0.0%
	Cerebral haemorrhage	0	0.0%	1	1.9%	0	0.0%	3	4.8%
Multi-organ failure		0	0.0%	0	0.0%	0	0.0%	0	0.0%
Ischemia of lower extremities		0	0.0%	0	0.0%	0	0.0%	0	0.0%
Aneurysm rupture		0	0.0%	0	0.0%	0	0.0%	0	0.0%
Vascular injury		1	1.9%	0	0.0%	5	7.9%	1	1.6%

8.B.(4) Safety

8.B.(4).1) Cerebrovascular disorder in patients with receiving a fenestrated stent graft(s)

The incidence of major complications is presented in Table 13 for fenestrated and unfenestrated stent grafts. The incidence within 30 days postoperative tended to be higher with fenestrated stent grafts than with unfenestrated ones. The incidence of cerebrovascular diseases was particularly high with fenestrated stent grafts.

Table 13. Incidence of major complications with fenestrated and unfenestrated stent grafts

		Fenestrated				Unfenestrated			
Number of subjects		79				38			
		≤30 days postoperative		>30 days and ≤12 months postoperative		≤30 days postoperative		>30 days and ≤12 months postoperative	
		No. of subjects	Incidence	No. of subjects	Incidence	No. of subjects	Incidence	No. of subjects	Incidence
Aneurysm-related death		1	1.3%	1	1.3%	0	0.0%	1	2.6%
All-cause death		1	1.3%	3	3.8%	0	0.0%	1	2.6%
Technical success		79	100.0%	-	-	37	97.4%	-	-
Major complications (total)		9	11.4%	10	12.7%	6	15.8%	1	2.6%
Heart disorder requiring surgical treatment		0	0.0%	0	0.0%	0	0.0%	0	0.0%
Long-term mechanical ventilation requiring tracheostomy		0	0.0%	1	1.3%	0	0.0%	1	2.6%
Renal disease newly requiring hemodialysis		0	0.0%	2	2.5%	0	0.0%	0	0.0%
Paraplegia or paraparesis lasting for ≥30 days postoperative		1	1.3%	1	1.3%	1	2.6%	0	0.0%
Pulmonary embolism		0	0.0%	1	1.3%	0	0.0%	0	0.0%
Cerebrovascular disease	Cerebral infarction	6	7.6%	0	0.0%	1	2.6%	0	0.0%
	Cerebral haemorrhage	0	0.0%	4	5.1%	0	0.0%	0	0.0%
Vascular injury		2	2.5%	1	1.3%	4	10.5%	0	0.0%

Since fenestrated stent grafts are deeply inserted into the ascending aorta, PMDA asked the applicant to explain the possibility of an increased risk for cerebrovascular disorders resulting from the migration of atheroma fragments, etc. at the aortic arch or thrombosis associated with the placement of Najuta Stent Graft.

The applicant's response:

In the clinical trial group, the incidence of cerebrovascular disorders within 12 months postoperative was 9% (11 of 117) in all subjects: 12.7% (10 of 79) in subjects receiving a fenestrated stent graft(s), and 2.6% (1 of 38) in subjects receiving an unfenestrated stent graft(s). In subjects receiving a fenestrated stent graft(s), the cerebrovascular disorders consisted of cerebral infarction (7.6% [6 of 79 subjects]) and cerebral haemorrhage (5.1% [4 of 79 subjects]).

The events of cerebral haemorrhage was unlikely to be related to Najuta Stent Graft, according to the investigators. All events of cerebral infarction occurred immediately after the implantation of Najuta Stent Graft, mostly in subjects receiving a fenestrated stent graft(s) (6 of 7 subjects). Because no subject receiving Najuta Stent Graft experienced unintended occlusion of an aortic arch branch(s), these cerebral infarctions are probably due to thromboembolism associated with maneuvering the delivery sheath, balloon catheter, or contrast enhanced catheter around aortic arch branches. The cerebral infarctions occurring in the clinical trial are adverse events for which the causal relationship to Najuta Stent Graft could not be ruled out.

Fenestrated Najuta Stent Graft is indicated mostly for lesion sites that cannot be fully treated with conventional thoracic stent grafts alone. This precludes a simple comparison of the risk for cerebral infarction between fenestrated Najuta Stent Graft and approved stent grafts.

The current standard treatment for lesion sites eligible for a fenestrated stent graft(s) is blood vessel prosthesis implantation, but recently hybrid TEVAR (i.e., the combination of thoracic endovascular aortic repair and revascularization, which secures the blood flow to the head and neck) has also been performed. It is therefore reasonable to discuss the risk of using fenestrated stent grafts by comprehensively comparing with hybrid TEVAR. To collect latest treatment results, the applicant conducted a literature search on experiences with hybrid TEVAR reported between 20[redacted] and 20[redacted]. A total of 388 patients treated with hybrid TEVAR were identified in 15 publications, excluding patients whose stent graft(s) is not located at Zone 2 or a more proximal zone and patients having the aorta itself replaced by an artificial blood vessel.[2]-[16] The incidence of cerebral infarction was comparable in subjects receiving a fenestrated stent graft(s) in the clinical trial (7.6%, 6 of 79 subjects) and patients receiving hybrid TEVAR (7.0%, 27 of 388 patients). With hybrid TEVAR, however, 33.3% (9 of 27) of patients with cerebral infarction died within 30 days. On the other hand, 5 of 7 subjects with cerebral infarction in the clinical trial recovered Activities of Daily Living (ADL) almost to the preoperative level. Most of the 7 subjects had relatively mild cerebral infarction, and none of them died within 30 days. The events of cerebral infarction in the clinical trial are less serious than those associated with hybrid TEVAR.

PMDA's view:
The incidence of cerebral infarction in subjects receiving a fenestrated stent graft(s) in the clinical trial (7.6%, 6 of 79 subjects) is not profoundly higher than the incidence with hybrid TEVAR in the literature (7.0%) or the incidence in historical controls receiving open surgery (6.5%, 6 of 86 subjects). In the clinical trial, no unintended occlusion of the aortic arch occurred, and only 1 of 6 subjects had a clinically significant sequelae of cerebral infarction, excluding subjects with poor preoperative ADL. These findings suggest that the risk for cerebral infarction in patients receiving a fenestrated stent graft(s) is not profoundly higher than that with conventional treatments. However, since the clinical trial evaluated only a limited number of subjects, the applicant should caution healthcare professionals about the risk for cerebral infarction and continue to collect post-marketing information.

8.B.(4).2) Aneurysm diameter expansion after 1 year postoperative

The submitted application data include only the results up to 1 year after implantation. According to malfunction reports during the trial, aneurysm diameter expansion occurred at ≥1 year postoperative.

PMDA asked the applicant to provide data on aneurysm diameter expansion occurring at ≥1 year postoperative.

The applicant presented data on the incidence and causes of aneurysm diameter expansion of ≥5 mm as of [redacted], 20[redacted] (Table 14).

Table 14. Incidence of aneurysm diameter expansion (including aneurysm diameter expansion newly identified after 24 months postoperative)

	Cause of diameter expansion	Entire	Fenestration	
			With	Without
12 months postoperative	Total	6.0% (7/117)	6.3% (5/79)	5.3% (2/38)
	Type I endoleak	1.7% (2/117)	2.5% (2/79)	0.0% (0/38)
	Type II endoleak	1.7% (2/117)	0.0% (0/79)	5.3% (2/38)
	Unknown	2.6% (3/117)	3.8% (3/79)	0.0% (0/38)
	Unconfirmed because of plain CT	0.0% (0/117)	-	0.0% (0/38)
24 months postoperative	Total	5.5% (3/55)	3.0% (1/33)	9.1% (2/22)
	Type I endoleak	0.0% (0/55)	0.0% (0/33)	0.0% (0/22)
	Type II endoleak	0.0% (0/55)	0.0% (0/33)	0.0% (0/22)
	Unknown	1.8% (1/55)	3.0% (1/33)	0.0% (0/22)
	Unconfirmed because of plain CT	3.6% (2/55)	-	9.1% (2/22)
36 months postoperative	Total	5.3% (1/19)	0.0% (0/8)	9.1% (1/11)
	Type I endoleak	0.0% (0/19)	0.0% (0/8)	0.0% (0/11)
	Type II endoleak	0.0% (0/19)	0.0% (0/8)	0.0% (0/11)
	Unknown	5.3% (1/19)	0.0% (0/8)	9.1% (1/11)
	Unconfirmed because of plain CT	0.0% (0/19)	-	0.0% (0/11)

PMDA's view:

Aneurysm diameter expansion of ≥5 mm occurred at ≥1 year postoperative in subjects receiving Najuta Stent Graft regardless of fenestration status: 6.0% (7 of 117 subjects) at Year 1 of implantation; 5.5% (3 of 55 subjects) at Year 2; and 5.3% (1 of 19 subjects) at Year 3 (Table 14). The incidence of aneurysm diameter expansion of ≥5 mm at ≥1 year postoperative with approved thoracic stent grafts was 9.3% to 21.6% and 0.0% to 6.3% up to 60 months in 2 studies of GORE TAG Thoracic Endoprosthesis,[17] 8.5% at 12 months with TALENT Thoracic Stent Graft System,[18] and 1.8% to 7.1% up to 24 months with COOK Zenith TX2 TAA Endovascular Graft.[19] These data suggest that the risk of aneurysm diameter expansion with Najuta Stent Graft is similar to that with the similar medical devices, although the long-term data (≥1 year postoperative) on Najuta Stent Graft are limited. In the clinical trial, however, acute aneurysm diameter expansion was detected in some patients by CT scan at ≥12 months of implantation. Attention should therefore be paid to the potential for aneurysm diameter expansion. In particular, in 15 subjects receiving Najuta Stent Graft, aneurysm diameter was expanded by ≥5 mm during the period from hospital discharge to ≥1 year postoperative. In 7 of the 15 subjects, the sealing zone at the proximal side was ≤21 mm (20 mm in 5 subjects, 21 mm in 2 subjects). On the basis of this finding, the applicant should caution healthcare professionals to carefully examine patients with a sealing zone length of ≤21 mm to determine their eligibility for Najuta Stent Graft, and to carefully follow them up after the implantation. The applicant should also provide training programs to ensure that healthcare professionals follow the cautions. Unidirectional CT may not be sufficient to measure aneurysm

diameter accurately; multidirectional assessment is required at least in patients showing no shrinking trend of aneurysm. The following 3 caution statements should be provided:

- Since the aneurysm diameter cannot be measured accurately by unidirectional slices alone, multidirectional scans should be performed to determine the tendency of aneurysm diameter expansion.
- Patients with aneurysm diameter expansion should be followed up by specialists, such as vascular surgeons.
- Patients with aneurysm diameter expansion should undergo periodic diagnostic imaging.

8.B.(4).3) Graft damage

The clinical trial showed no graft damage at 12 months postoperative. At 37 months, however, 1 type III endoleak due to graft damage was reported. PMDA asked the applicant to explain the cause of this malfunction and risk reduction measures.

The applicant's response:

The durability test revealed no damage, etc., although stronger stress was applied to the graft in the test than in routine clinical practice. The graft damage identified at 37 months was likely explained by stress concentrated at a point where the edge of the Z stent skeleton contacted the graft, because of the placement in an unnatural shape resulting from the excessive extension of the Z stent. In the clinical trial, 4 of 5 subjects with a Z stent implanted in an unnatural shape showed a shrunk or shrinking aneurysm. The remaining 1 subject had aneurysm diameter expansion of 6 mm at 36 months postoperative, although no endoleak was observed. These subjects should be carefully followed up for aneurysm diameter and graft damage, including the necessity of additional intervention. The following cautions will be included in the package insert as a risk reduction measure: "Najuta Stent Graft should not excessively be pulled toward the distal side while placing the device" and "When the aneurysm length exceeds 5 cm, 2 stent grafts should be used to prevent 1 stent graft from being excessively extended."

PMDA's view:

The durability test of Najuta Stent Graft, conducted under the same conditions as those for the approved stent grafts, revealed no particular concerns. This means that Najuta Stent Graft has a durability required for thoracic aorta stent grafts. Najuta Stent Graft does not regain the original shape once it is deformed beyond the elasticity of stainless steel. Nevertheless, since no such deformation was noted in the integrity test after stent graft deployment, the stress analysis of the stent grafts (FEM analysis), the animal study in sheep, etc., Najuta Stent Graft can be used without any problems if the basic implantation procedures are followed properly.

In the local compression test, the stent grafts were compressed until they were crushed, but no plastic deformation occurred. The graft damage in the trial was likely explained by placement of the stent graft in an unnatural shape, resulting from excessive extension of the Z stent. These findings suggest that, because of its raw materials and structural characteristics, Najuta Stent Grafts does not suffer plastic deformation even when compressed radially until being crushed, but the device may not regain the original shape once it is deformed longitudinally beyond the elasticity limit of stainless steel. Healthcare professionals should be cautioned that stent grafts may be damaged by excessive stress if they are extended unnaturally.

8.B.(5) Rationale for proposed models and operating procedures

PMDA's view:

The appropriateness of the proposed models and operating procedures of Najuta Stent Graft has been verified through the clinical trial. No adverse event attributable to the wrong selection of the product models has been reported. In addition, the applicant documented the procedures that had not been specified at the time of conducting the clinical trial, and added the documented procedures in the "Operation Method or Usage Method" section of the submission dossier. To assess the appropriateness of the proposed models, there is no other option but to use the results of the nonclinical tests on fitting performance and the results of the clinical trial, because there are anatomical differences between humans and sheep. The nonclinical tests on the basic fitting performance, including kink resistance, radial force, and migration resistance, showed no concerns. The clinical trial also revealed that the incidence of adverse events and malfunctions with Najuta Stent Graft (e.g., death due to device incompatibility, aneurysm diameter expansion, endoleak, and migration) was not higher than that with the approved stent grafts. Therefore, at present, there are no particular concerns about the proposed models and operating procedures.

8.B.(6) Stent grafts not used in the clinical trial

The clinical trial did not evaluate all 952 models of Najuta Stent Graft because it was infeasible to examine all models. The applicant provided the rationale for including the models not used in the clinical trial in the present application, in terms of different effects on safety (aneurysm diameter expansion and migration) according to the difference in (a) skeletal type, (b) fenestrated type, and (c) stent graft diameter.

The applicant's explanation:

(a) Stent skeleton models not used in the clinical trial

A short sealing zone and a poor fitting of a stent graft to the inner wall of the blood vessel may cause aortic aneurysm diameter expansion. The stent skeleton that is most likely to cause this event is large arch model 7LW, which is intended to be used in patients with a strongly tortuous distal aortic arch.

Large arch model 7LW was used in 22 of 117 subjects in the clinical trial who had a short sealing zone and progressive elongation, resulting in a high incidence of aneurysm diameter expansion of 13.6% (3 of 22 subjects). Aneurysm diameter expansion observed in patients receiving model 7LW was likely caused by several anatomical factors, including strongly curved or tortuous sealing zone as well as a short sealing zone.

Less curved or less tortuous models appear to be associated with a higher risk for migration. The stent skeletons with the highest risk of migration are descending large models 06, 07, 08, 09, and 10. Of 117 subjects in the trial, 10 received descending models 06, 07, 08, and 10, without migration. Descending model 09 was not used in the clinical trial. Model 09 differs from the other descending large models only in torsion direction between Z stents, and has a similar curve and torsion angle to the other models. This means that the risk of migration does not differ substantially between model 09 and the other models.

(b) Fenestrated types not used in the clinical trial

Endoleak may cause aneurysm diameter expansion. The worst-case model in terms of the risk for endoleak is probably the 38-mm CL3 (3 holes) model, which provides the largest ratio of the opening width of the fenestration to the graft diameter. None of the 3 subjects receiving the 38-mm CL3 model had endoleak, indicating that all fenestrated types of Najuta Stent Graft have a clinically relevant ability to seal blood flow. Having a fenestration(s) is very unlikely to cause stent graft migration.

(c) Stent graft size not used in the clinical trial

The 42-mm stent graft was not used in the clinical trial. According to the incidences of aneurysm diameter expansion with different stent graft sizes in the clinical trial, the incidence of aneurysm diameter expansion did not depend on stent graft size, indicating no correlation between the stent graft size and aneurysm diameter expansion.

The risk for stent graft migration was evaluated *in vitro*. The 42-mm stent graft was also considered to have a clinically relevant resistance to migration.

PMDA's view:

Stent graft models not used in the clinical trial should be approved only when they meet the following basic requirements:

(A) The stent graft models used in the clinical trial were implanted under the worst possible conditions based on the anatomical characteristics (e.g., position, diameter, length, curve, and torsion) of target blood vessels treatable with Najuta Stent Graft.

(B) The study results of the stent grafts used in the trial, including those used under the conditions described in (A), have not shown any problems.

PMDA's view on the applicant's explanations (a) to (c) shown above:

(a) Stent skeleton models not used in the clinical trial

Requirement (A) is met because the clinical trial used the stent skeleton considered associated with the clinical worst-case scenario in terms of the risk for aneurysm diameter expansion and stent graft migration.

As for Requirement (B), the incidence of aneurysm diameter expansion was as high as 13.6% (3 of 22) of subjects receiving large arch model 7LW (the worst-case model in terms of aneurysm diameter expansion), and as high as 20.6% (7 of 34) of subjects with a sealing length of ≤21 mm (21 and 20 mm). The trial suggested the risk for aneurysm diameter expansion even after 1 year after graft implantation. However, Najuta Stent Graft, including the models not used in the clinical trial, can be approved, provided that appropriate risk reduction measures are taken (e.g., cautioning physicians to carefully determine eligibility of individual patients for the device and to carefully follow them up after implantation), because Najuta Stent Graft offers a treatment option other than open surgery to patients with distal aortic arch aneurysm, and because of the following reasons:

(i) Among the subjects receiving large arch model 7LW, only those with a sealing zone length of ≤21 mm had aneurysm diameter expansion.
(ii) None of the subjects had stent graft migration after 3 months of implantation.
(iii) The results of the stent skeletons used in the clinical trial suggest that none of the stent skeletons not used in the trial are possibly associated with a particularly high incidence of aneurysm diameter expansion.
(iv) An appropriate model of Najuta Stent Graft should be selected depending on the anatomical characteristics of the aorta of each patient.

(b) Fenestrated types not used in the clinical trial

Requirement (A) is met because the applicant's discussion of the clinical worst-case scenario assumed in the clinical trial is reasonable. As for Requirement (B), although only 3 subjects received the worst-case model, the clinical trial results of the model had no problems. There are no particular problems with providing the fenestrated types not used in the clinical trial to patients in clinical practice.

(c) The 42-mm stent graft not used in the clinical trial

Requirement (A) is not met because the 42-mm stent graft, the worst-case model, was not used in the clinical trial. However, there are no particular problems with providing the 42-mm stent graft to patients in clinical practice, for the following reasons explained by the applicant:

(a) There is no correlation between the stent graft size and aneurysm diameter expansion.

(b) In a migration resistance test, the 42-mm stent graft showed similar results to approved thoracic stent grafts.

(c) The measured force (mean 1.85 N) in the migration resistance test is greater than the force (approximately 0.055 N) a blood flow puts on a stent in humans, calculated from the literature data.[20]

(d) No stent graft migration was reported after 3 months postoperative, other than 3 events of migration that occurred in relation to the delivery sheath or concomitant devices during operation.

8.B.(7) Intended use and indication

PMDA asked the applicant to explain why the proposed intended use and indication include no criteria for reference vessel diameters. The applicant responded that they would modify the intended use and indication as shown below. PMDA accepted the applicant's response.

Intended Use and Indication (Underline denotes addition.)

Najuta Stent Graft is used in the treatment of thoracic aortic aneurysms that meet all of the following anatomical requirements:

1. An appropriate iliac/femoral artery access route is available.
2. Normal portions of the aorta (without any aneurysm) that meet the following criteria are available as sealing zones at both the proximal and distal sides of an aneurysm:
   - The length of the normal vessel between the bifurcation of the left common carotid artery and the aortic aneurysm is ≥20 mm. (When the left subclavian artery is not covered, the length of the normal blood vessel between the bifurcation of the left subclavian artery and the aortic aneurysm is ≥20 mm.)
   - The length of the normal vessel between the bifurcation of the celiac artery and the aortic aneurysm is ≥20 mm.
   - <u>The normal vessel at the sealing zones of the proximal and distal sides of the aneurysm has a diameter of ≥20 mm and <38 mm.</u>

8.B.(8) Training program, etc.

PMDA asked the applicant to consider revising the training program and practice standards of Najuta Stent Graft, because this device has a different manipulation technique and implantation strategy from those for approved thoracic stent grafts, and because the practice standards for TEVAR with approved stent grafts do not suffice.

The applicant's response:

Physicians trained in the clinical trial achieved a technical success rate of 99.1% (116 of 117 subjects). In the post-marketing settings, however, Najuta Stent Graft is expected to be used by physicians less experienced than those participating in the trial. For these reasons, the proposed training program has a tougher goal than the training provided to physicians participating in the clinical trial (see below). In addition, the standard placement technique for Najuta Stent Graft, called "pull-through," is included in the training program, because the lack of experience in "pull-through" may increase the incidence of stent graft migration and cerebral infarction.

Training goal in the clinical trial

To succeed in endovascular repair in ≥2 patients, including at least 1 patient who requires a fenestrated stent graft, in the presence of a supervising physician.

Training goal in the post-marketing settings

To succeed in endovascular repair in ≥3 patients, including at least 2 patients who require a fenestrated stent graft, in the presence of a supervising physician.

The latest version of the "Practice Standards for Stent Grafting of Thoracic Aortic Aneurysms" established by the Japanese Committee for Stentgraft Management, does not take into account stent grafts covering branch vessels of the aortic arch, such as Najuta Stent Graft. The applicant plans to establish (a) qualification standards for physicians performing thoracic endovascular aortic repair using stent grafts covering branch vessels and (b) qualification standards for physicians who supervise the performing physicians, based on discussions with the Japanese Committee for Stentgraft Management.

PMDA's view:

The proposed post-marketing training program requires physicians to achieve a tougher goal than the training provided in the clinical trial, and includes instructions on "pull-through," the standard placement technique for Najuta Stent Graft. This is appropriate because physicians who will use Najuta Stent Graft in the post-marketing settings are less experienced than those participating in the clinical trial, and because Najuta Stent Graft requires unique manipulation technique/placement strategy not shared by the approved thoracic stent grafts. The outline of the proposed draft training program is acceptable although its details should be discussed further.

It is appropriate to establish qualification standards for physicians performing thoracic endovascular aortic repair using stent grafts covering branch vessels, and for physicians who supervise the performing physicians, based on discussions with the Japanese Committee for Stentgraft Management.

8.B.(9) Post-marketing surveillance etc.

The applicant plans to conduct post-marketing surveillance in patients implanted with fenestrated Najuta Stent Graft, to identify patient characteristics, evaluate the safety and efficacy of the device, and obtain information regarding malfunctions immediately. The planned sample size is 650 patients. The planned surveillance period is 3 years. Patients who receive Najuta Stent Graft during the surveillance period will be followed up for long-term outcome up to 5 years of implantation.

PMDA's view:

Najuta Stent Graft has 952 models (types) resulting from various combinations of stent skeletons, curves, and the number of fenestrations, and the most suitable model should be selected for each patient. The applicant should confirm whether the appropriate model has been selected for individual patients after the market launch. The post-marketing surveillance should therefore cover all patients receiving Najuta Stent Graft regardless of fenestration status until information has been collected from a certain number of patients. Fenestrated stent grafts, which are characteristic of Najuta Stent Graft, have not been approved overseas and there is only limited experience of their use in Japan. Their safety and efficacy should be evaluated more closely in the surveillance. Najuta Stent Graft was shown to have short-term efficacy and safety in the clinical trial, but its long-term efficacy and safety remain to be evaluated. The safety and efficacy up to 5 years should therefore be evaluated in the post-marketing surveillance (a use-results survey), as with the approved stent grafts.

Based on the above, PMDA asked the applicant to modify the post-marketing surveillance protocol. The applicant responded that they appropriately modify the protocol accordingly. PMDA accepted the applicant's response, concluding that the outline of the proposed draft post-marketing surveillance protocol was basically reasonable although its details should be discussed further.

8.B.(10) Results of expert discussion and measures taken

At the Expert Discussion, the expert advisors agreed on the clinical position of Najuta Stent Graft in that fenestrated models have the advantage of providing a low invasive treatment to patients with an insufficient landing (sealing) zone for conventional endovascular stent graft repair, for example patients with an aneurysm at the lesser curvature side just below the left subclavian artery or left common carotid artery. The expert advisors made the following comments:

> Elderly patients often have a strongly curved aortic arch, which may prevent a stent graft from adhering to the lesser curvature side of the aortic arch, resulting in an endoleak. As fenestrated Najuta Stent Graft can be implanted at the ascending aorta, it would provide an excellent sealing at the proximal side of an aneurysm located at the lesser curvature side.

The expert advisors' comments on the risk of cerebral infarction with fenestrated models:

- The incidence of cerebral infarction was higher in patients using fenestrated models. The higher incidence should be considered due to the already increased risk of cerebral infarction associated with aneurysms treatable only with a fenestrated stent graft(s).
- The risk for cerebral infarction should be assessed based on the severity.

The expert advisors supported the following PMDA's conclusion on the risk reduction measures for aneurysm diameter expansion:

> Using the package insert, the applicant should inform healthcare professionals that a proximal sealing zone length of ≤21 mm is associated with a high incidence of aneurysm diameter expansion and may be associated with an increased risk of aneurysm diameter expansion even after 1 year of implantation. The applicant should also provide this information through training programs.

The expert advisors' comments on CT scans for assessment of aneurysm diameter expansion:

- Unidirectional CT is sufficient to assess the diameter expansion of aneurysms if they have not expanded in diameter or if they are located in the descending aorta. Multidirectional CT is required to assess the diameter expansion of aneurysms at the greater curvature of the distal aortic arch, saccular aneurysms at the lesser curvature, etc.
- Some patients require multidirectional slice images to measure aneurysm diameter. In view of busy outpatient settings, however, it is practical to limit multidirectional CT to patients with a suspected tendency of aneurysm diameter expansion.
- Since multiplanar imaging is commonly performed to follow up aortic aneurysms at the thoracic aortic arch, all patients receiving Najuta Stent Graft should be examined for aneurysm diameter expansion by multiplanar 3D reformation imaging, etc.

PMDA explained that at least patients with no shrinking tendency of aneurysm require multidirectional CT to appropriately identify aneurysm diameter expansion; this view was supported by the expert advisors. PMDA concluded that CT imaging should be performed every 6 months in patients with a tendency of aneurysm diameter expansion or every 1 year in patients with no tendency of aneurysm diameter expansion; this conclusion was supported by expert advisors. The expert advisors commented that the status of aneurysm diameter expansion may be followed by non-specialists as well as specialists (i.e., vascular surgeons), but CT images should be reviewed by specialists.

Based on the above opinions from expert advisors, PMDA instructed the applicant to caution healthcare professionals about these issues through the package insert and training sessions. The applicant responded that they take measures accordingly.

The expert advisors supported the PMDA's conclusion that the stent graft models not used in the clinical trial may also be approved.

The expert advisors also supported the PMDA's conclusion on the post-marketing surveillance, and offered the following comments:

- The surveillance should be conducted to assess not only stent graft migration and aneurysm diameter expansion, but also the patency of branch vessels (the brachiocephalic artery and left common carotid artery) with blood flow maintained by a fenestration(s).
- Collecting information regarding the curve of the aortic arch will contribute to the safe use of Najuta Stent Graft in a few years.

PMDA instructed the applicant to add the assessment of branch vessel patency to the post-marketing surveillance. The applicant responded that they take measures accordingly.

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

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

The New Medical Device Application Data were subjected to a document-based compliance inspection and data integrity assessment in accordance with the provision of paragraph 5 of Article 14 of the Pharmaceutical Affairs Act. As a result, no particular problems were identified. PMDA thus concluded that there were no obstacles to conducting its regulatory review based on the application documents submitted.

PMDA's conclusion concerning the results of document-based and on-site QMS inspection

A QMS inspection was conducted in accordance with the provision of paragraph 6 of Article 14 of the Pharmaceutical Affairs Act. PMDA concluded that there were no particular problems.

V. Overall Evaluation

Najuta Stent Graft is a stent graft system for the treatment of thoracic aortic aneurysm. The stent graft consists of a stainless-steel stent (Z stent skeleton) and a polytetrafluoroethylene (PTFE) graft ([redacted]) sewn on the stent. It is loaded into the delivery sheath in advance. The regulatory review of Najuta Stent Graft focused on the following issues: (a) cerebrovascular disorders in patients receiving a fenestrated stent graft(s); (b) aneurysm diameter expansion at ≥1 year postoperative, and (c) qualification standards for physicians and medical institutions using Najuta Stent Graft, training program, etc.

PMDA's conclusion on issues (a) to (c) based on discussions with the expert advisors:

(a) Cerebrovascular disorders in patients using a fenestrated stent graft(s)

The incidence of cerebral infarction in subjects receiving a fenestrated stent graft(s) in the clinical trial (7.6%, 6 of 79 subjects) is not profoundly higher than the incidence with hybrid TEVAR in the literature (7.0%) or the incidence in historical controls receiving open surgery (6.5%, 6 of 86 subjects). In the clinical trial, no unintended occlusion of the aortic arch occurred, and only 1 of 6 subjects had a clinically significant sequelae of cerebral infarction, excluding subjects with poor preoperative ADL. These findings suggest that the risk for cerebral infarction in patients receiving a fenestrated stent graft(s) is not profoundly higher than that with conventional treatments. However, since the clinical trial evaluated only a limited number of subjects, the applicant should caution healthcare professionals about the risk for cerebral infarction and continue to collect post-marketing information.

(b) Aneurysm diameter expansion after 1 year postoperative

Aneurysm diameter expansion of ≥5 mm occurred at ≥1 year postoperative in subjects receiving Najuta Stent Graft regardless of fenestration status: 6.0% (7 of 117 subjects) at Year 1 of implantation; 5.5% (3 of 55 subjects) at Year 2; and 5.3% (1 of 19 subjects) at Year 3. Available data suggest that the risk of aneurysm diameter expansion with Najuta Stent Graft is similar to that with the similar medical devices, although the long-term data (≥1 year postoperative) on Najuta Stent Graft are limited. In the clinical trial, however, acute aneurysm diameter expansion was detected in some patients by CT scan at ≥12 months of implantation. Attention should therefore be paid to the potential for aneurysm diameter expansion. In particular, in 15 subjects receiving Najuta Stent Graft, aneurysm diameter was expanded by ≥5 mm during the period from hospital discharge to ≥1 year postoperative. In 7 of the 15 subjects, the sealing zone at the proximal side was ≤21 mm (20 mm in 5 subjects, 21 mm in 2 subjects). On the basis of this finding, the applicant should caution healthcare professionals to carefully examine patients with a sealing zone length of ≤21 mm to determine their eligibility for Najuta Stent Graft, and to carefully follow them up after the implantation. The applicant should also provide training programs to ensure that healthcare professionals follow the cautions. Unidirectional CT may not be sufficient to measure aneurysm diameter accurately; multidirectional assessment is required at least in patients showing no shrinking tendency of aneurysm. The following 3 caution statements should be provided:

- Since the aneurysm diameter cannot be measured accurately by unidirectional slices alone, multidirectional scans should be performed to determine the tendency of aneurysm diameter expansion.
- Patients with aneurysm diameter expansion should be followed up by specialists, such as vascular surgeons.
- Patients with aneurysm diameter expansion should undergo periodic diagnostic imaging.

Condition of approval 3 (see below) is required because long-term results from many patients implanted with Najuta Stent Graft are important.

(c) Qualification standards for physicians and medical institutions performing endovascular stent graft repair, training program, etc.

It is appropriate to establish qualification standards for physicians performing thoracic endovascular aortic repair using stent grafts covering branch vessels, and for physicians who supervise the performing physicians, based on discussions with the Japanese Committee for Stentgraft Management.

The proposed post-marketing training program requires physicians to achieve a tougher goal (i.e., to succeed in endovascular repair in at least 3 patients, including at least 2 patients who require a fenestrated stent graft model, in the presence of a supervising physician) than the training provided in the clinical trial, and the program includes instructions on "pull-through," the standard placement technique for Najuta Stent Graft. This is appropriate because physicians who will use Najuta Stent Graft in the post-marketing settings are less experienced than those participating in the clinical trial, and because Najuta Stent Graft requires unique manipulation technique/placement strategy not shared by the approved thoracic stent grafts. The outline of the proposed draft training program is acceptable although its details should be discussed further.

Najuta Stent Graft must be used by physicians who have been trained well in advance, to ensure its efficient and safe use. In addition, prompt surgical interventions is required if aneurysm rupture is caused by implantation of Najuta Stent Graft. For these reasons, Conditions of Approval 1 and 2 (see below) are required.

On the basis of the above results, PMDA has concluded that Najuta Stent Graft may be approved for the intended use shown below with the following conditions of approval.

Intended Use and Indication

Najuta Stent Graft is used in the treatment of thoracic aortic aneurysms that meet all of the following anatomical requirements:

1. An appropriate iliac/femoral artery access route is available.
2. Normal portions of the aorta (without any aneurysm) that meet the following criteria are available as sealing zones at both the proximal and distal sides of an aneurysm:
    - The length of the normal vessel between the bifurcation of the left common carotid artery and the aortic aneurysm is ≥20 mm. (When the left subclavian artery is not covered, the length of the normal blood vessel between the bifurcation of the left subclavian artery and the aortic aneurysm is ≥20 mm.)
    - The length of the normal vessel between the bifurcation of the celiac artery and the aortic aneurysm is ≥20 mm.

- The normal vessel at the sealing zones of the proximal and distal sides of the aneurysm has a diameter of ≥20 mm and <38 mm.

Conditions of Approval

1. The applicant is required to take appropriate measures to ensure that the product is used by physicians with sufficient knowledge and experience in endovascular repair of thoracic aortic aneurysms at medical institutions able to provide treatment of possible complications of endovascular stent graft repair.
2. The applicant is required to take appropriate measures to ensure that the product is used only for the indication by qualified physicians (i.e., those who meet the criteria specified in Condition of Approval 1) who, through training, etc., have acquired sufficient skills in maneuvering the product and sufficient knowledge of complications of the procedures.
3. The applicant is required to perform use-results surveys (including an extension survey of patients participating in the submitted clinical trial) covering all patients treated with the product until data from a specific number of patients have been accrued; report the results of long-term outcome analysis to the Pharmaceuticals and Medical Devices Agency; and take appropriate measures as necessary.

As Najuta Stent Graft is a new performance medical device, the 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.

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