

December 6, 2017

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

### **Report on the Deliberation Results**

<b>Category</b>	Medical Products 04, Orthopedic Products
<b>Term Name</b>	Thyroid cartilage fixation device
<b>Brand Name</b>	TITANBRIDGE
<b>Applicant</b>	Nobelpharma Co., Ltd.
<b>Date of Application</b>	June 30, 2017 (Application for marketing approval)

#### **Results of deliberation**

The results of deliberation of the Committee on Medical Devices and *In-vitro* Diagnostics on December 6, 2017 are as described below. The Committee concluded that the results should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product should be designated as a medical device subject to the use-results survey and approved with the following condition. The product is not classified as a biological product or a specified biological product.

The use-results survey period should be 6 years.

#### **Condition of Approval of the Marketing Application**

The applicant is required to take necessary measures (e.g., provision of training sessions) in cooperation with relevant academic societies, so that surgeons with adequate knowledge of and experience in type II thyroplasty will adequately acquire the skills to use the product and knowledge of adductor spasmodic dysphonia and then use the product in accordance with the intended use and method of use.

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

## Review Report

November 21, 2017  
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.

<b>Category</b>	Medical Products 04, Orthopedic Products
<b>Term Name</b>	Thyroid cartilage fixation device
<b>Brand Name</b>	TITANBRIDGE
<b>Applicant</b>	Nobelpharma Co., Ltd.
<b>Date of Application</b>	June 30, 2017
<b>Items Warranting Special Mention</b>	Orphan Medical Device and <i>Sakigake</i> Designations
<b>Reviewing Office</b>	Office of Medical Devices III

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## Review Results

November 21, 2017

<b>Category</b>	Medical Products 04, Orthopedic Products
<b>Term Name</b>	Thyroid cartilage fixation device
<b>Brand Name</b>	TITANBRIDGE
<b>Applicant</b>	Nobelpharma Co., Ltd.
<b>Date of Application</b>	June 30, 2017

### Results of the Review

TITANBRIDGE is a hinged bridge made of titanium (titanium bridge), which is used to keep the split thyroid ala apart in type II thyroplasty for improvement in the symptoms of adductor spasmodic dysphonia.

The applicant submitted the non-clinical data, which included the data on the physical and chemical properties, biological safety, stability and durability, and performance of TITANBRIDGE. The data submitted showed no particular problems.

The applicant submitted the clinical data, namely the results from an investigator-initiated Japanese clinical trial (hereinafter referred to as the clinical trial). This trial was a prospective, multicenter, open-label, uncontrolled clinical trial conducted to evaluate the safety and clinical efficacy of type II thyroplasty with titanium bridges in 21 patients with adductor spasmodic dysphonia.

The Japanese version of Voice Handicap Index-10 (VHI-10) served as the primary endpoint for the clinical trial. The VHI-10 is accepted internationally as a means to assess patients' perception of the severity of their voice disorder and recommended by the Japan Society of Logopedics and Phoniatics.

In the clinical trial, the change from baseline in the mean VHI-10 total score at 13 weeks after surgery in the 21 patients was -18.905. This change was greater than the value pre-specified at the time of trial design (-9.6). Thus, the efficacy of type II thyroplasty with titanium bridges was demonstrated by the clinical trial. The change was much greater than the clinically significant

difference between healthy volunteers/non-dysphonic patients and dysphonic patients reported in the literature, and thus this finding adequately indicates the clinically significant efficacy of type II thyroplasty with titanium bridges.

Safety evaluation revealed no serious adverse events in the 21 patients. Main adverse events included pain associated with surgical procedure. There were no malfunctions such as device failure or device-related adverse events.

The efficacy and safety of type II thyroplasty with TITANBRIDGE can be evaluated based on the data submitted. PMDA discussed the evaluation comprehensively, taking into account the comments raised in the Expert Discussion. Given that TITANBRIDGE is an orphan medical device and that no satisfactory treatment for adductor spasmodic dysphonia has been established in Japan, PMDA has concluded that offering TITANBRIDGE to healthcare professionals in clinical practice is meaningful.

Selection of eligible patients and compliance with precautions for type II thyroplasty are important to ensure the efficacy and safety of type II thyroplasty with TITANBRIDGE. For this reason, TITANBRIDGE should be appropriately used for the surgical procedure in eligible patients by surgeons with adequate knowledge of and experience in adductor spasmodic dysphonia and type II thyroplasty with TITANBRIDGE. Thus, PMDA has concluded that this advice should be imposed as a condition of approval.

As a result of its review, PMDA has concluded that TITANBRIDGE may be approved for the intended use shown below, with the following condition, and that this application should be subject to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

**Intended Use**

Improvement in the symptoms of adductor spasmodic dysphonia

**Condition of Approval**

The applicant is required to take necessary measures (e.g., provision of training sessions) in cooperation with relevant academic societies, so that surgeons with adequate knowledge of and experience in type II thyroplasty will adequately acquire the skills to use the product and knowledge of adductor spasmodic dysphonia and then use the product in accordance with the intended use and method of use.

## Review Report

November 21, 2017

### Product for Review

<b>Category</b>	Medical Products 04, Orthopedic Products
<b>Term Name</b>	Thyroid cartilage fixation device
<b>Brand Name</b>	TITANBRIDGE
<b>Applicant</b>	Nobelpharma Co., Ltd.
<b>Date of Application</b>	June 30, 2017
<b>Proposed Intended Use</b>	Improvement in the symptoms of adductor spasmodic dysphonia
<b>Items Warranting Special Mention</b>	Orphan Medical Device and <i>Sakigake</i> Designations

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## List of Abbreviations

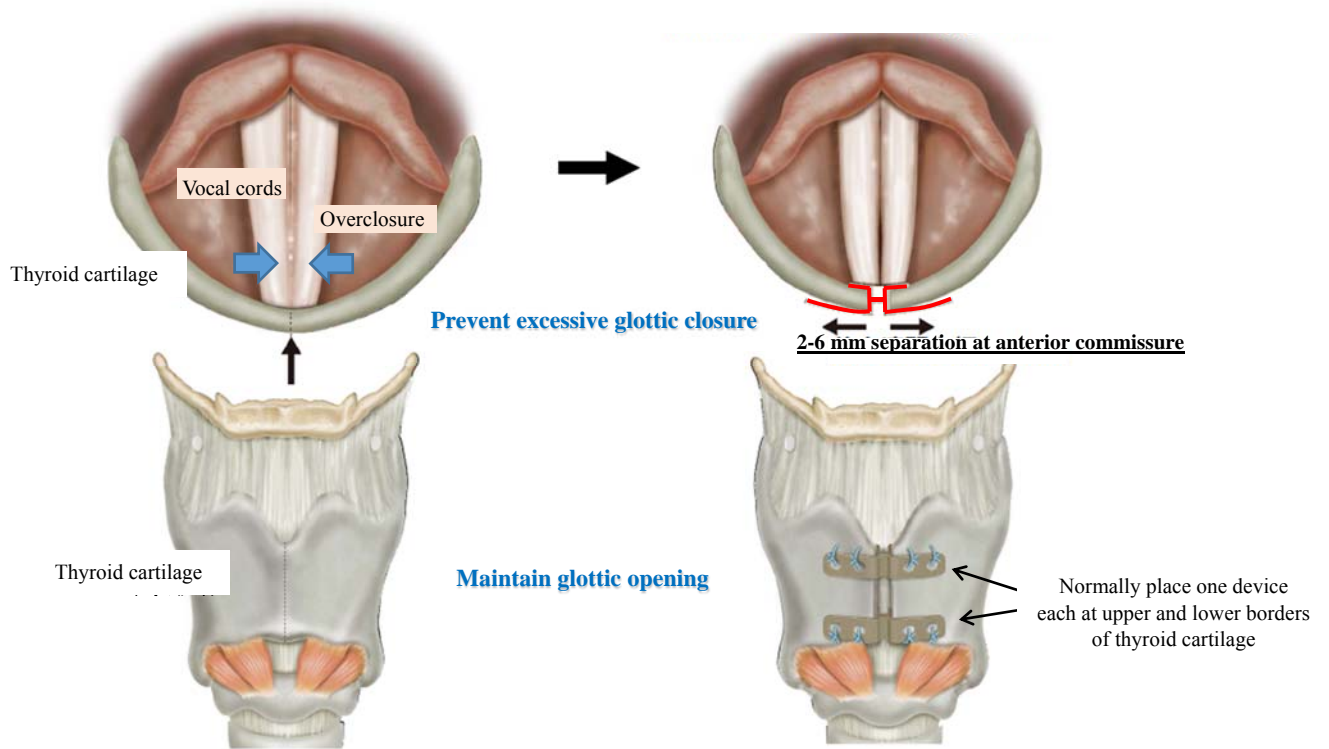
AMED	Japan Agency for Medical Research and Development
DVB	Degree of Voice Breaks
FAS	Full Analysis Set
HNR	Harmonics to Noise Ratio
JIS	Japanese Industrial Standards
LLT	Lowest Level Term
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Effect Model for Repeated Measures
SD	Standard Deviation
SDF0	Standard Deviation of Fundamental Frequency
SEM	Scanning Electron Microscope
SOC	System Organ Class
VHI	Voice Handicap Index
VHI-10	Voice Handicap Index-10

## **I. Product Overview**

Adductor spasmodic dysphonia is a voice disorder characterized by involuntary and intermittent spasms of the intrinsic muscles of the larynx during phonation, which cause hyperadduction of the vocal cords and overclosure of the glottis. Type II thyroplasty for the treatment of adductor spasmodic dysphonia is a surgical procedure in which the thyroid cartilage is split in the midline and the thyroid alae are pulled apart at the anterior commissure, to which bilateral thyroarytenoid muscles attach, before being fixed, so that the glottis does not close too tightly (Figure 1).

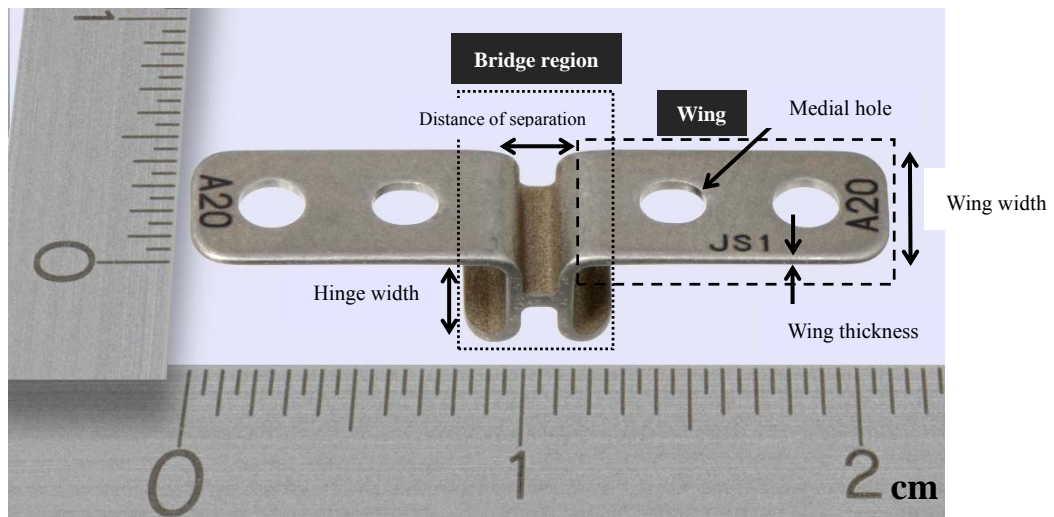
TITANBRIDGE is a fixation device made of titanium, which is used for the above-mentioned surgical procedure. Its structure is characteristic. It consists of the bridge region that serves to separate the thyroid ala divided in the midline and to keep the thyroid alae apart and the wings that have the holes through which sutures are anchored to the thyroid alae (hinged bridge structure) (Figure 2). TITANBRIDGE, submitted for marketing approval, comes in various sizes: 3 different widths of the hinge part of the bridge (3.02, 4.02, and 5.02 mm) available for the thickness of the thyroid ala divided in the midline, and 2 different widths of the wing (3.0 and 5.0 mm) available for the length of the thyroid ala. TITANBRIDGE also comes in 7 different sizes for the distance of separation (2.0, 2.5, 3.0, 3.5, 4.0, 5.0, and 6.0 mm), so that the optimal distance of separation can be chosen based on the patient's voice quality. Normally, TITANBRIDGE is placed at the upper and lower borders of the thyroid cartilage (one piece each).

An estimated 4900 to 9800 people in Japan<sup>1,2</sup> have adductor spasmodic dysphonia for which TITANBRIDGE is indicated. There is no curative treatment, and patients have persistent difficulty in social life. At the time of regulatory submission, surgical treatment with TITANBRIDGE is expected to have a permanent effect in improving the severity of voice disorder in this patient population. Thus, TITANBRIDGE received orphan medical device designation on September 2, 2016 because it was considered a medical device of particularly high medical need. TITANBRIDGE also received *Sakigake* designation on February 10, 2016 for the following reasons: (i) Therapy with TITANBRIDGE is based on a novel principle different from those of existing therapies, and (ii) TITANBRIDGE is a medical device that have been developed in Japan, ahead of the rest of the world.



Adapted from the figures provided by Kumamoto University

**Figure 1. Method of Use of TITANBRIDGE (Type II thyroplasty)**



**Figure 2. Appearance of TITANBRIDGE (hinged bridge structure)**



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

The data submitted in 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 have declared that they do not fall under Item 5 of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

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

#### **1.1 History of development**

##### ***1.1.A. Summary of the submitted data***

Adductor spasmodic dysphonia is a type of functional dysphonia which is not associated with any organic abnormality or palsy of the larynx. It is an intractable disease of unknown cause, categorized as focal dystonia. Involuntary and intermittent spasms of the intrinsic laryngeal muscles during phonation lead to hyperadduction of the vocal cords and overclosure of the glottis. This causes a complex of symptoms, including voice stoppages or breaks, strained-strangled, effortful speech, and a hoarse voice, which vary among patients. Patients have difficulty in speaking and communicating others at work and in everyday life and thereby suffer from psychological distress. Adductor spasmodic dysphonia significantly affects patients' social life. Despite the seriousness of the disease, there is no curative treatment. Although there is no definitive evidence to support its efficacy in patients with adductor spasmodic dysphonia, voice training (voice therapy) as a non-invasive, conservative therapy has been performed to reduce muscle tension in the larynx during phonation.

Furthermore, other therapies are available for patients who do not respond to voice therapy (see Table 1).

**Table 1. Comparison of treatments for adductor spasmodic dysphonia in patients who do not respond to voice therapy**

Treatment Features	Type II thyroplasty (TITANBRIDGE)	Botulinum toxin type A injection therapy	Thyroarytenoid myectomy
Invasiveness	Moderate	Low	High
Anesthesia	Local anesthesia	None	General anesthesia
Duration of effect	Permanent	Temporary (3-4 months)	Basically permanent
Severity of symptoms for which treatment is indicated	Mild to Severe	Mild to Severe	Moderate to Severe
Features	The operation is performed under local anesthesia so that the voice can be monitored to check improvement in symptoms during surgery while the surgeon adjusts the distance of separation of the thyroid ala divided in the midline.	This is an internationally employed therapy, but unapproved in Japan. Patients treated with botulinum toxin injections may experience post-treatment symptoms such as swallowing and breathing difficulties for a while.	A hoarse voice associated with vocal cord atrophy and scarring after surgery persists.

In Japan, thyroarytenoid myectomy has been used so far. In this procedure, the thyroarytenoid muscle causing vocal disorder is excised as much as possible, with direct laryngoscopy under general anesthesia. However, this surgical technique has been performed at only a limited number of medical institutions for reasons such as its high invasiveness and the persistence of a hoarse voice associated with vocal cord atrophy and scarring after surgery<sup>3,4</sup> [see the right column in Table 1].

On the other hand, an internationally employed low-invasive therapy is local injection of botulinum toxin type A into the intrinsic laryngeal muscles to reduce involuntary movements of the vocal cords, though it is unapproved in Japan. A high response rate with this therapy has been reported, but the duration of action is limited to 3 to 4 months.<sup>5,6</sup> Patients treated with botulinum toxin injections may experience post-treatment symptoms such as swallowing and breathing difficulties for a while [see the middle column in Table 1].

Type II thyroplasty is a surgical procedure in which the thyroid cartilage is split in the midline, the thyroid alae are pulled apart while preserving the anterior commissure (i.e., the attachment of the thyroarytenoid muscle), and then they are fixed, so that the glottis does not close too tightly even with strong contraction of the intrinsic laryngeal muscles during phonation. This surgical procedure is less invasive than the existing surgical therapy (thyroarytenoid myectomy) and is

expected to provide a permanent treatment effect. The operation is performed under local anesthesia so that the voice can be monitored while the surgeon adjusts the distance between the separated thyroid cartilage. Depending on the patient's postoperative course, a revision surgery can also be performed for a better treatment effect. In light of these advantages, this surgical procedure would be beneficial [see the left column in Table 1].

Type II thyroplasty was developed by Isshiki et al. in 2001.<sup>7</sup> Various materials were explored to identify a suitable material for fixation of the split thyroid cartilage (fixation material) in the surgical procedure. Fixation materials initially used included autologous cartilage grafts, silicon block, and titanium miniplates. However, because failure of fixation materials, thyroid cartilage fracture, and other problems occurred in some patients, the development of the dedicated fixation materials was considered desirable for the success of this surgical procedure. In 2002, pure titanium was chosen as a raw material from the standpoints of biocompatibility and durability, and the development of a hinged bridge most suitable for keeping the thyroid alae apart (i.e., a titanium bridge) was initiated.

Isshiki et al. accumulated clinical experience with Type II thyroplasty with titanium bridges (41 patients) to prove its efficacy.<sup>8,9</sup> Initially, titanium bridges were made available in various specifications for individual patients. The wing, bridge region, etc., of the device varied in thickness, width, and length. In 2006, the titanium bridge specification (the specification for the investigational device) was established following 2 clinical research programs conducted by Sanuki et al. at Kumamoto University.<sup>10</sup> In parallel with these clinical research programs (47 patients), clinical experience was accumulated at 8 sites in Japan, including Kumamoto University (338 patients). In the above studies, a total of 385 patients underwent Type II thyroplasty with titanium bridges by December 2014 (the preceding clinical research programs).

Clinical use of titanium bridges for type II thyroplasty and the evolution of the specification are shown in Table 2.

**Table 2. Clinical use of titanium bridges for type II thyroplasty and evolution of specification**

Time	Clinical use	Titanium bridge specification, etc.
December 2002 to December 2005	Clinical experience by Isshiki et al. at Kyoto Voice Surgery Center (41 patients reported in the literature)	A hinged bridge structure. Various specifications for individual patients. The wing, bridge region, etc. of the device varied in thickness, width, and length.
August 2006 to December 2014	Two clinical research programs at Kumamoto University (47 patients reported in the literature)	Initially, various specifications for individual patients, as was the case of the procedure by Isshiki et al. The specification for the investigational device was established based on the accumulated clinical experience. In the second clinical research program, all patients underwent type II thyroplasty with the investigational device.
Around 2002* to December 2014	Clinical experience at 8 sites in Japan, including Kumamoto University (338 patients)	Various specifications for individual patients as was the case of the procedure by Isshiki et al. The specification for the investigational device used in the clinical research programs at Kumamoto University was also employed.
July 2015 to March 2017	Investigator-initiated clinical trial at 4 sites in Japan, including Kumamoto University (21 patients)	Specification for the investigational device

\* Based on the results of survey on patients who underwent revision surgery at 8 sites in Japan. The survey included clinical experience with titanium bridges developed by Isshiki et al. The exact starting date is unclear.

In the preceding clinical research programs, revision surgery was performed in 19 patients whose symptoms such as hoarse voice and strangled voice were expected to improve. Revision surgeries revealed that the wing had broken in its medial hole in 11 patients. However, this fracture was not associated with any sign of recurrence of pretreatment vocal symptoms or any adverse event in the surrounding tissue. Analysis of the devices recovered (from 2 patients) revealed fatigue fracture at the site bent by the surgeon to fit the thyroid cartilage of the patient when inserting the titanium bridge. In addition to the cases of device failure in the preceding clinical research programs, fracture of the bridge region was noted in 1 non-Japanese patient. The presumed cause of this fracture was as follows: Because the thick thyroid cartilage of the patient precluded insertion of the prepared titanium bridges, the surgeon shaved the thyroid cartilage to insert the titanium bridges. The bridge region was exposed to excessive force during or after surgery.

On the basis of the results of the preceding clinical research programs, Sanuki et al. began to work toward commercialization of the titanium bridge. They initiated “a study on the effectiveness of type II thyroplasty with titanium bridges in the treatment of adductor spasmodic dysphonia,” which was adopted as both a research project on rare/intractable diseases under the Health and Labor Sciences Research Grants and a practical research project for rare/intractable diseases funded by Japan Agency for Medical Research and Development (AMED) in 2014. This study

was intended to determine the product specification for commercialization of the titanium bridge, in parallel with evaluation in an investigator-led Japanese clinical trial initiated in 2015 to evaluate “type II thyroplasty with titanium bridges for the treatment of adductor spasmodic dysphonia” (the clinical trial).

For efficacy evaluation of type II thyroplasty with titanium bridges, the Japanese version of Voice Handicap Index-10 (VHI-10) served as the primary endpoint for the clinical trial. The VHI-10 is accepted internationally as a means to assess patients’ perception of the severity of their voice disorder and recommended by the Japan Society of Logopedics and Phoniatrics.<sup>11-14</sup> The change from baseline in the mean VHI-10 score at 13 weeks after surgery in 21 patients was  $-18.905$ . This change was greater than the value ( $-9.6$ ) pre-specified at the time of trial design based on the outcome of botulinum toxin injection reported in an overseas study.<sup>15</sup> The clinical trial demonstrated the efficacy of type II thyroplasty with titanium bridges.

However, the titanium bridges used in the clinical trial (the investigational device) have the specification that was optimized based on clinical experience gained until December 2014. Table 3 shows the changes made to the specification for commercialization (i.e., the differences between the proposed product [TITANBRIDGE] and the investigational device).

The appropriateness of the specification changes was assessed in terms of the clinically desired shape of TITANBRIDGE to fit the thyroid ala of patients and its strength required to keep the thyroid alae apart. The assessment took into account cases of wing fractures (11 patients) and bridge fracture (1 patients) occurring in the preceding clinical research programs involving 385 patients. Normally, the thyroid cartilage is routinely and repeatedly exposed to forces during glottic opening and closure, swallowing, and other movements. Compressive forces act on the bridge region, and bending moments on the wings. The shape of TITANBRIDGE of the changed specification was assessed to determine if the device has fatigue durability to withstand these forces, referring to fatigue testing of metallic plates to be used at load-bearing sites in the orthopedic field. As a result, the bridge region was shown to have fatigue durability to withstand            cycles of loading greater than the load resulting in compression fracture of the thyroid cartilage, and the wings were shown to have improved bending durability, compared to the wings of the investigational device. Thus, TITANBRIDGE was shown to have sufficient strength for clinical use.

The present application was submitted, based on the results of the clinical trial and assessment of the appropriateness of the specification changes for commercialization.

**Table 3. Specification changes  
(differences between Titanbridge and the investigational device)**

Changes		TITANBRIDGE	Investigational device
Design of Wing	Overall wing shape	2 types One is the same type as the investigational device, and the other type has a shorter width of the wing, with retention of the same strength. The latter one is made available for patients with a short vertical length of the thyroid cartilage (e.g., women).	██████
	Medial hole shape	2 types One hole shape is the ellipse with a shorter diameter in the direction of width of the wing for increased strength of the wing, and the other is the perfect circle with a shortened diameter corresponding to the decreased width of the wing, with retention of the same strength. The latter is made available for patients with a short vertical length of the thyroid cartilage (e.g., women).	██████ (██████)
Design of bridge region		3 types One is the same type as the investigational device, and other 2 types with increased width and thickness of the hinge part. The latter types are made available for patients with thick thyroid cartilage (e.g., well-built men).	██████

**1.2 Use in foreign countries**

**1.2.A Summary of the submitted data**

TITANBRIDGE is not approved or licensed overseas.

**2. Design and development**

**2.1 Performance and safety specifications**

**2.1.A Summary of the submitted data**

The proposed specifications for performance of TITANBRIDGE include static compressive strength and compressive fatigue strength of the bridge region as well as appearance. The proposed specifications for safety include ethylene oxide sterilization residuals and biological safety. The applicant submitted data to justify these specifications.

**2.1.B Outline of the review conducted by PMDA**

PMDA reviewed the data including those presented in Section “2.5 Data to support performance” and concluded that there is no particular problem with the proposed product specifications.

## **2.2 Physical and chemical properties**

### **2.2.A Summary of the submitted data**

In order to evaluate its quality, a pure titanium plate (a raw material of TITANBRIDGE) was subjected to tensile testing, which assessed tensile strength, proof stress, and elongation. The plate was shown to conform to pure titanium Class 2 as specified by JIS H 4600 “Titanium and titanium alloys - Sheets, plates and strips.”

### **2.2.B Outline of the review conducted by PMDA**

PMDA reviewed the data on the physical and chemical properties of TITANBRIDGE, and concluded that there is no particular problem.

## **2.3 Biological safety**

### **2.3.A Summary of the submitted data**

Only raw materials that conform to pure titanium Class 2 as specified by JIS H 4600 (“Titanium and titanium alloys - Sheets, plates and strips”) are used for TITANBRIDGE. As listed in Attachment 1 of PFSB/ELD/OMDE Notification No. 0730-10, dated July 30, 2010, “Review Guideline for internal fixation screws and internal fixation plates” (hereinafter referred to as “the guideline for internal fixation plates etc.”), pure titanium that conforms to JIS H 4600 is the specification material used for internal fixation screws and plates. Although the intended use and method of use of TITANBRIDGE are different from those of internal fixation screws and plates, the data of biological safety testing were omitted because the site of contact and the duration of contact are the same as those of the previously approved products.

### **2.3.B Outline of the review conducted by PMDA**

PMDA reviewed the biological safety of TITANBRIDGE, and concluded that there is no particular problem with omitting biological safety testing.

## **2.4 Stability and durability**

### **2.4.A Summary of the submitted data**

TITANBRIDGE is made of a metallic material (pure titanium) only, and its stability is known. TITANBRIDGE is not subjected to radiation sterilization, nor does the material deteriorate. For the above reasons, stability and durability testing was omitted.

### **2.4.B Outline of the review conducted by PMDA**

Pure titanium has been used in various medical applications and its stability and durability are known. PMDA therefore concluded that there is no particular problem with omitting stability and

durability data.

## 2.5 Data to support performance

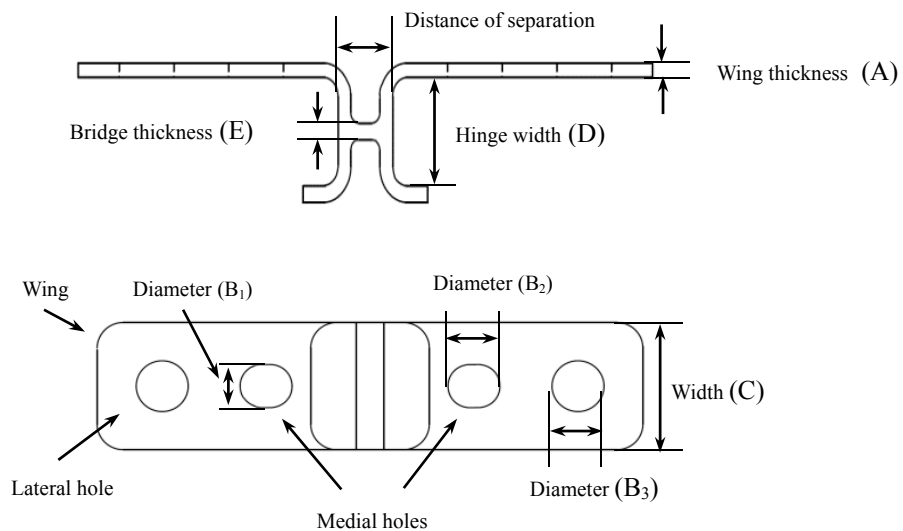
### 2.5.A Summary of the submitted data

The applicant's explanation about the data to support the performance of TITANBRIDGE is presented in the following sections.

#### 2.5.A.(1) Setting of specification for TITANBRIDGE

Based on the preceding clinical research programs, the basic specifications for TITANBRIDGE to fit the thyroid cartilage of patients were established for commercialization. The basic specifications consist of 4 types: the standard specification (increased strength of the wings compared to the investigational device), 2 specifications for patients with thick thyroid cartilage, and 1 specification for patients with short thyroid cartilage. The right type can be chosen depending on the size of thyroid cartilage of patients. Aside from these basic specifications, the bridge region is available for 7 different distances of separation (2.0, 2.5, 3.0, 3.5, 4.0, 5.0, and 6.0 mm) so that the optimal distance of separation can be chosen based on the patient's voice quality.

The shape and structure of TITANBRIDGE and the name of each part are shown in Figure 3, and 4 basic specifications are shown in Table 4. The underlined dimensions in Table 4 represent the changes from those of the investigational device.



**Figure 3. Shape and structure of TITANBRIDGE and name of each part**



**Table 4. Investigational device and the basic specifications for TITANBRIDGE**

Basic specifications		Dimensions (mm)	Wing thickness (A)	Medial hole diameter (B <sub>1</sub> /B <sub>2</sub> )	Lateral hole diameter (B <sub>3</sub> )	Width (C)	Hinge width (D)	Bridge thickness (E)
TITANBRIDGE	Standard specification product		■	■	■	5.0	3.02	■
	Product for patients with short thyroid cartilage		■	■	■	<u>3.0</u>	3.02	■
	Product for patients with thick thyroid cartilage (1)		■	■	■	5.0	<u>4.02</u>	■
	Product for patients with thick thyroid cartilage (2)		■	■	■	5.0	<u>5.02</u>	■
Investigational device * Not applicable to the proposed product (TITANBRIDGE)			■	■	■	■	■	■

**2.5.A.(1).1) Standard specification product**

Of 385 patients included in the preceding clinical research programs, 19 underwent revision surgery because their symptoms such as hoarse voice and strangled voice were expected to further improve. Revision surgeries revealed that the wing had broken in its medial hole in 11 patients. The device failures in these patients resulted in no tissue damage around the site of device insertion or associated symptoms such as pain. Although their voice needed some adjustment, pretreatment vocal symptoms did not recur. Titanium bridges used in the preceding clinical research programs varied in specification. The devices used included those equivalent to the investigational device and those prepared for individual patients. The most mechanically fragile specification (the worst case) could not be identified in the clinical research programs.

The titanium bridges recovered (2 patients) were analyzed for the cause of device failure. The fracture surface was subjected to scanning electron microscopy (SEM), which revealed fatigue fracture at the site bent by the surgeon to fit the thyroid cartilage of the patient when inserting the titanium bridge. Reverse bending weakens the material and decreases its fatigue durability. Whether the surgeon had bent and unbent the titanium bridge could not be determined, but its possibility cannot be ruled out.

The wings of TITANBRIDGE have the holes through which sutures are anchored to the thyroid ala divided in the midline, so that the device cannot move upward or downward, away from its original position. In addition, cicatrization of the tissues around the wings allows firmer fixation of TITANBRIDGE. The worst-case scenario is that the device breaks at the medial holes of its both wings in the early post-operative phase before cicatrization. Even in such a case, the thyroid alae will be kept apart and the treatment effect will not be reduced markedly, as long as the bridge

region does not deviate from the midline split site. Device failure cases in 11 patients included 1 case of displacement due to a blow to the head and 1 case of deviation requiring adjustment because of a hoarse voice. However, no major displacement associated with device failure occurred in any patient, nor did vocal symptoms recur. Based on these findings, broken holes are unlikely to pose a major risk.

Although these 11 patients had no tissue damage around the site of device insertion or other failure-related events, the risk of unnecessary revision surgery should be minimized, assuming the worst-case scenario in which the fragments of the broken wing may move substantially to stimulate the peripheral tissues and then cause pain. Since bending of TITANBRIDGE to fit the thyroid cartilage is important for the appropriate fixation of TITANBRIDGE, its wings should have sufficient bending strength.

Based on these malfunctions detected in the preceding clinical research programs and the analysis of the devices recovered due to malfunctions, the following specification changes were made for commercialization to define the standard specification product: (i) The shape of the medial hole of the wing was changed to an ellipse, and (ii) the wing thickness (A) was increased by ■ mm compared to the investigational device to increase the strength of the wing.

#### **2.5.A.(1).2) Product for patients with thick thyroid cartilage**

Besides 385 patients included in the preceding clinical research programs, 1 non-Japanese patient with adductor spasmodic dysphonia underwent surgical therapy with titanium bridges. Fracture of the bridge region was found in the patient. The thyroid cartilage of this patient was thicker than the width of the hinge part of the titanium bridge prepared, and the thyroid cartilage was shaved to the hinge width for insertion of the titanium bridges. This procedure was different from that used in the preceding clinical research programs.

In type II thyroplasty, keeping the thyroid alae apart is important for improvement in vocal symptoms. Failure of the bridge region precludes from keeping the thyroid alae apart, thereby leading to recurrence of the symptoms. In order to uniformly distribute the force on the bridge region and appropriately keep the thyroid alae apart without causing flexure or failure, the devices with different hinge widths to suit the thickness of the thyroid cartilage that supports the bridge region should be prepared for stabilization of the devices.

If the thyroid cartilage is shaved as in this case, its stability will not be ensured and the bridge region will be subjected to unexpected anisotropic forces, increasing the risk of flexure and failure.

Hence, 2 product specifications for patients with thick thyroid cartilage were established to ensure that the device can be inserted without shaving of the thyroid cartilage. Compared to the standard specification product, the hinge width (D) was increased by ■ or ■ mm, and accordingly, the bridge thickness (E) was increased by ■ or ■ mm, respectively.

**2.5.A.(1).3) Product for patients with short thyroid cartilage**

Since patients of small build such as women have short thyroid cartilage (length in a direction parallel to its midline), the width (C) of the device needs to be shortened so that one piece each can be placed at the upper and lower borders of the thyroid cartilage. The product specification for patients with short thyroid cartilage was established as follows: The width (C) was shortened by ■ mm compared to the standard specification product, and in order to prevent the associated reduced strength of the wings, the wing thickness (A) was increased by ■ mm, and the medial and lateral holes are perfect circles with a diameter (B<sub>1</sub>/B<sub>2</sub>, B<sub>3</sub>) of ■ mm.

TITANBRIDGE is a fixation device made of titanium to keep the thyroid alae apart. The device was tested to verify its performance, referring to the guideline for internal fixation plates etc., which is the review guideline used for therapy with metallic osteosynthesis devices in the orthopedic field. Because the bridge region is subjected to compressive stress from both sides and cyclic stress caused by movements of intrinsic and extrinsic laryngeal muscles or swallowing, static compression and compression fatigue testing of the bridge region was conducted in accordance with the performance and safety specifications, referring to JIS T 0312 “Testing methods for bending properties of metallic osteosynthesis devices” and JIS T 0313 “Testing methods for compression bending properties of metallic osteosynthesis devices.” A specification limit of ■N was chosen, based on the literature on assessment of an injury of the thyroid cartilage caused by mechanical loading and other articles.<sup>16,17</sup> The results of strength testing of the products of different specifications are shown in Table 5.

**Table 5. Results of strength testing of the bridge region of TITANBRIDGE**

Test and strength	Static compression test 0.2% offset load (upper row) Maximum load (lower row)	Compression fatigue test Maximum load
Basic specifications		
Standard specification product	■ N ■ N	■ N
Product for patients with short thyroid cartilage	■ N ■ N	■ N
Product for patients with thick thyroid cartilage (1)	■ N ■ N	■ N
Product for patients with thick thyroid cartilage (2)	■ N ■ N	■ N

Static compression testing (the left column in Table 5) showed satisfactory results for all basic specification products. The load resulting in fracture of the bridge region was much greater than the load resulting in an injury of the thyroid cartilage reported in the literature (█ N). TITANBRIDGE is inserted while separating the thyroid ala divided in the midline. The surgeon does not have to apply excessive force on TITANBRIDGE, and the product that withstands this load has sufficient strength for clinical use.

Compression fatigue testing (the right column in Table 5) also showed satisfactory results for all basic specification products. The maximum load at which the specimen withstood the specified number of cycles was much greater than the load resulting in an injury of the thyroid cartilage (█ N). The maximum load determined in this test cannot be kept applied on the bridge region of TITANBRIDGE in every-day settings unless a large load resulting in fracture of the thyroid cartilage is constantly kept applied externally on the site of insertion of the product in clinical use. According to the literature and other references,<sup>18,19</sup> the cyclic load applied on the thyroid cartilage during swallowing and other laryngeal movements in every-day settings is estimated at approximately 0.05 to 0.1 N. TITANBRIDGE has sufficient fatigue strength to withstand this level of loading, as the thyroid cartilage is not a weight-bearing site in every-day settings. TITANBRIDGE does not cause an injury of the thyroid cartilage due to their different strengths. This can also be explained by no abnormalities in cartilaginous tissue detected in 11 patients who underwent revision surgery and reported malfunctions in the preceding clinical research programs. The above findings have demonstrated that TITANBRIDGE has sufficient performance required for the bridge region in clinical use. Because the bridge thickness and width of the standard specification product are identical to those of the investigational device, the results of the performance of the bridge region of the standard specification product support the performance of the investigational device. Thus, the data submitted have shown that there are no problems with clinical use of the investigational device.

For commercialization, TITANBRIDGE was intended to have increased strength of the wings compared to the investigational device. Representative products with different basic specifications for the wings were selected as the specimens, and they were defined as “the standard specification product” and “the product for patients with short thyroid cartilage.” Referring to JIS T 0312 “Testing methods for bending properties of metallic osteosynthesis devices” and JIS T 0313 “Testing methods for compression bending properties of metallic osteosynthesis devices,” the specimens were subjected to static 3-point bending testing and 3-point bending fatigue testing. Table 6 shows the results for the products with different

specifications. Both basic specification products were shown to have increased strength compared to the investigational device.

**Table 6. Results of strength testing of the wing of the product**

Test and strength	Static 3-point bending test 0.2% offset load (upper row) Maximum load (lower row)	3-point bending fatigue test Maximum load
Basic specifications		
Standard specification product	■ N ■ N	■ N
For patients with short thyroid cartilage	■	■ N
Investigational device * Not applicable to the proposed product (TITANBRIDGE)	■ N ■ N	■ N

In these tests, the wings of the specimen were fixed to the supporting jig with screws, which is different from the condition of clinical use where the wings of TITANBRIDGE are sutured and fixed on the thyroid cartilage. In clinical use, TITANBRIDGE is fixed on the cartilage with nylon sutures through the holes of the wings. This allows a looser fixation than that with screws and a reduction in the estimated cyclic load applied on the wings during swallowing or other laryngeal movements. Even if cyclic load is applied on the wings during swallowing or other laryngeal movements, the maximum load determined in the fatigue test is greater than that for both TITANBRIDGE and the investigational device. Thus, the wings of TITANBRIDGE were shown to have sufficient performance required for clinical use.

On the other hand, the surgeon may bend TITANBRIDGE to fit the thyroid cartilage of the patient by applying a load greater than the loads applied during the strength testing. Generally, metallic plates for use in the orthopedic field, which are similar to TITANBRIDGE, are also bent. Since bending decreases the mechanical strength of such devices, the package insert and other instructions for use include precautions against excessive and reverse bending. The cases of failures of the wings of the titanium bridges were analyzed in the preceding clinical research programs, and the analysis of the devices recovered also revealed fatigue fracture at the bending site. Bending by the surgeon may have affected the strength of the device. The investigational device has the specification optimized based on clinical experience accumulated during the preceding clinical research programs. For commercialization, the titanium bridge should have a reduced risk of device failure compared to the investigational device, while it should still allow for the minimum necessary degree of bending to fit the thyroid cartilage of the patient, for stable implantation of the device.

From these standpoints, the applicant decided to increase the strength of the wings of TITANBRIDGE compared to the investigational device by modifying the wing thickness and other specifications. In addition, precautionary advice about bending was to be provided, as with metallic plates for use in the orthopedic field.

### ***2.5.B Outline of the review conducted by PMDA***

The applicant's explanation about wing fractures in 11 of 19 patients who underwent revision surgery in the preceding clinical research programs:

Wing fractures were found accidentally when patients underwent revision surgery for further improvement in voice quality. The lack of efficacy of type II thyroplasty with titanium bridges or reduced efficacy after surgery was not observed in any of these 11 patients, except for displacement due to a blow. None of these patients had adverse events etc. associated with stimulation at the device failure site. In all patients, the entire titanium bridge including the broken portion was covered with cicatricial tissue, and the bridge region remained fixed in the appropriate position on the thyroid cartilage. The efficacy of the titanium bridge is the ability of its bridge region to keep the thyroid alae apart. Although the wings broke, the bridge regions remained fixed appropriately. Pretreatment vocal symptoms did not recur. As described above, there were no efficacy or safety concerns. Meanwhile, 1 case of bridge fracture was a special case where the thyroid cartilage thicker than the hinge width of the titanium bridge used was shaved for insertion of the titanium bridges. This procedure was different from the usual one.

PMDA asked the applicant to explain the causes of wing and bridge fractures.

The applicant's explanation:

The fracture surfaces of the wings were analyzed by SEM. Based on the analysis results, the applicant concluded that fatigue fracture, starting from the vicinity of the medial hole, was induced by cyclic bending stress. The package insert and other instructions for use will contain the following advice: If TITANBRIDGE needs to be bent for insertion to fit the thyroid cartilage of the patient, then bend the product gradually using an instrument etc., do not reverse bend, and avoid hole deformation during bending, in order to prevent a decrease in the strength of the wing. The bridge region was considered to have broken because the force of intrinsic and extrinsic laryngeal muscles and vibration applied on the bridge region were imbalanced between the right and left sides.

PMDA's view:

The distance of separation of the thyroid alae is adjusted for insertion of TITANBRIDGE while

checking improvement in symptoms. TITANBRIDGE is gradually covered with cicatricial tissue and fixed on the thyroid cartilage appropriately. During this process, the distance of separation of the thyroid alae may need some adjustment even if optimized at the time of insertion. The applicant claimed that the cases of revision thyroplasty in 19 patients in the preceding clinical research programs were not necessarily associated with device failures, and that they underwent revision surgery for further improvement in symptoms. The applicant's claim is understandable.

SEM analysis showed that wing fractures in the preceding clinical research programs were attributable to fatigue fracture. This finding was reflected on the product design. For example, the wing thickness was increased for commercialization to increase the strength of TITANBRIDGE compared to the investigational device. Furthermore, TITANBRIDGE is bent for insertion to fit the thyroid cartilage of the patient. Bending is performed also for metallic plates used in the orthopedic field. Thus, inclusion of similar precautions regarding the method of use in the package insert is appropriate.

The applicant's opinion (the critical region for the efficacy of TITANBRIDGE is the bridge region. As long as failure of the bridge region does not occur and the correct distance of separation is maintained, wing fractures do not necessarily lead to reduced efficacy of TITANBRIDGE) is acceptable. The attempt to increase the wing strength compared to the investigational device should be appropriate to reduce unnecessary revision surgeries such as replacement due to failures. Non-clinical testing showed the increased strength of TITANBRIDGE compared to the investigational device. Hence, PMDA instructed the applicant to specify the product strength in the application; the shapes, dimensions, and locations of the wings and holes in the "Shape, Structure, and Principle" section and the method of forming the raw material into TITANBRIDGE and surface treatment method in the "Manufacturing Process" section. The applicant accepted the instruction.

Validation of the specification required for the bridge region of TITANBRIDGE is considered appropriate for the following reasons (a) and (b).

- (a) Referring to the guideline for internal fixation plates etc., static compression and compression fatigue testing of the bridge region was conducted under conditions simulating clinical use to verify its strength.
- (b) The specification limit required for the bridge region of TITANBRIDGE was set at ■■■ N based on the strength of thyroid cartilage.

Moreover, the test results showed that all specification products meet the acceptance criteria required for clinical use.

On the basis of the above, PMDA concluded that the validation of the specifications required for

the product and the required strength specification are appropriate.

## **2.6 Data to support method of use**

### **2.6.A Summary of the submitted data**

The data to support the method of use were omitted because the method of use of TITANBRIDGE was validated by the clinical trial.

### **2.6.B Outline of the review conducted by PMDA**

PMDA concluded that there is no particular problem with omitting data to support the method of use, for the following reasons: (i) Since the wings of TITANBRIDGE may be bent for insertion to fit the thyroid alae, surgeons who intend to use the product will be informed of the method for safe bending and necessary precautions to be taken; and (ii) the method of use of TITANBRIDGE was validated in the clinical trial, and no malfunctions or failures occurred during implantation.

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

### **3.A Summary of the submitted data**

The applicant submitted a declaration of conformity to confirm that the product meets the requirements for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Ministerial Announcement No.122 of 2005 issued by Ministry of Health, Labour and Welfare).

### **3.B Outline of the review conducted by PMDA**

PMDA reviewed the conformity of TITANBRIDGE to the Essential Principles.

Article 1 specifies the assumptions, etc., for the design of medical devices (especially, the assumed level of technical knowledge and experience that the user of the medical device has, and to what extent education and training should be given to the user).

PMDA's conclusion on the conformity of TITANBRIDGE to Article 1:

As later described in Sections "6.(3).B Efficacy," "6.(4).B Safety," and "6.(5).B Provision of information regarding use of TITANBRIDGE," selection of patients eligible for therapy with TITANBRIDGE and the procedure for separating the split thyroid ala are important. Since surgeons who intend to use TITANBRIDGE must have knowledge and skills to ensure that the



product can keep the thyroid alae apart, the information proposed initially by the applicant was considered inadequate. PMDA thus instructed the applicant to take necessary measures, and the applicant accepted it.

On the basis of the above, PMDA comprehensively evaluated the conformity of TITANBRIDGE to the Essential Principles, and concluded that there is no particular problem.

#### **4. Risk management**

##### ***4.A Summary of the submitted data***

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

##### ***4.B Outline of the review conducted by PMDA***

PMDA reviewed the risk management information/data, and concluded that there is no particular problem.

#### **5. Manufacturing process**

##### ***5.A Summary of the submitted data***

The manufacturing process information/data submitted consisted of those on manufacturing process and facilities, quality control, and sterilization method and sterility assurance. The information submitted also included the method of forming the raw material into TITANBRIDGE and surface treatment, which are critical process steps to assure the required strength of TITANBRIDGE.

##### ***5.B Outline of the review conducted by PMDA***

PMDA reviewed the manufacturing process information/data, and concluded that there is no particular problem.

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

##### ***6.A Summary of the submitted data***

The clinical data were obtained from an open-label, uncontrolled, multicenter trial conducted in 21 patients at 4 sites in Japan between July 29, 2015 and March 29, 2017 (the date when the last patient completed the 52-week follow-up after surgery) to evaluate the efficacy and safety of type II thyroplasty with titanium bridges in the treatment of adductor spasmodic dysphonia. Key inclusion and exclusion criteria are summarized in Table 7.

The basic specification for the investigational device (titanium bridges) used in this clinical trial was established based on the preceding clinical research programs.

**Table 7. Trial population and key inclusion and exclusion criteria**

Trial population	<p>Patients with adductor spasmodic dysphonia</p> <p>Patients who have a diagnosis of adductor spasmodic dysphonia and who have vocal symptoms for <math>\geq 1</math> year after the onset of apparent symptoms. For patient selection, it is necessary to differentiate adductor spasmodic dysphonia from hyperfunctional dysphonia with similar symptoms. Patients with no response to voice training (voice therapy) under the guidance of an otolaryngologist or a speech-language-hearing therapist.</p>
Key inclusion criteria	<p>(1) Patients with a diagnosis of adductor spasmodic dysphonia confirmed by an otolaryngologist certified by the Oto-Rhino-Laryngological Society of Japan</p> <p>(2) Patients with adductor spasmodic dysphonia who have had effortful speech or voice breaks, as assessed subjectively or objectively, for <math>\geq 1</math> year.</p> <p>(3) VHI-10 score <math>\geq 20</math></p> <p>(4) Non-responders to voice therapy performed before giving consent</p>
Key exclusion criteria	<p>(1) Dysphagia, laryngeal paralysis, or any organic lesion of the vocal cords</p> <p>(2) Previous surgery for adductor spasmodic dysphonia</p> <p>(3) Local injection of botulinum toxin type A into the intrinsic laryngeal muscles within 6 months prior to giving consent</p> <p>(4) Serious concomitant diseases (e.g., heart disease, pulmonary fibrosis, interstitial pneumonia, bleeding tendency, poorly controlled hypertension or diabetes)</p> <p>(5) Surgery under general anesthesia scheduled during the trial period or surgery performed within the past 4 weeks</p> <p>(6) Participation in any other interventional study within 12 weeks prior to giving consent, or planned participation in such a study during the trial period after enrollment in the trial</p> <p>(7) A history of hypersensitivity to pure titanium</p>

### 6.A.(1) Efficacy evaluation

The primary efficacy endpoint for the clinical trial was the change from baseline in VHI-10 scores at 13 weeks after type II thyroplasty with titanium bridges. As shown in Table 8, the VHI is a 30-item questionnaire to assess voice disorders. Each question is scored from 0 to 4 according to the patient's response. Higher scores (a maximum score of 120) indicate greater voice-related handicap, and patients with higher VHI scores are clinically assessed as having increased disease severity. VHI-10 is a shorter version of VHI consisting of the major 10 questions (1, 3, 10, 14, 16, 17, 19, 22, 23, 25), with a maximum score of 40. Although VHI is compatible with VHI-10, simpler VHI-10 is more commonly used in clinical practice. Therefore VHI-10 was used as the primary endpoint for the clinical trial.

**Table 8. Japan Society of Logopedics and Phoniatics' version of VHI<sup>13</sup>**

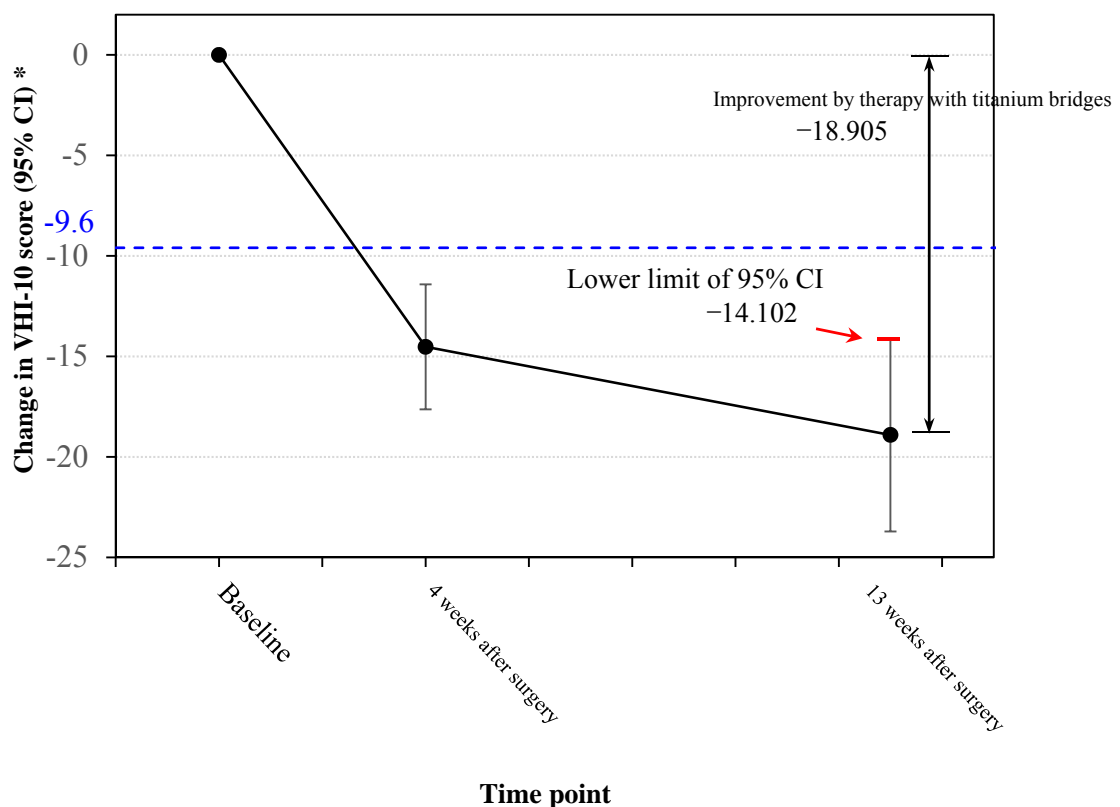
VHI questionnaire

These are statements that many people have used to describe their voices and the effects of their voices on their lives. Circle the response that indicates how frequently you have the same experience in the past 2 weeks.

0: never, 1: almost never, 2: sometimes, 3: almost always, 4: always

1. My voice makes it difficult for people to hear me.
2. I run out of air when I talk.
3. People have difficulty understanding me in a noisy room.
4. The sound of my voice varies throughout the day.
5. My family has difficulty hearing me when I call them throughout the house.
6. I use the phone less often than I would like to.
7. I am tense when talking to others because of my voice.
8. I tend to avoid groups of people because of my voice.
9. People seem irritated with my voice.
10. People ask, "What's wrong with your voice?"
11. I speak with friends, neighbors, or relatives less often because of my voice.
12. People ask me to repeat myself when speaking face-to-face.
13. My voice sounds creaky and dry.
14. I feel as though I have to strain to produce voice.
15. I find other people don't understand my voice problem.
16. My voice difficulties restrict my personal and social life.
17. The clarity of my voice is unpredictable.
18. I try to change my voice to sound different.
19. I feel left out of conversations because of my voice.
20. I use a great deal of effort to speak.
21. My voice is worse in the evening.
22. My voice problem causes me to lose income.
23. My voice problem upsets me.
24. I am less outgoing because of my voice problem.
25. My voice makes me feel handicapped.
26. My voice "gives out" on me in the middle of speaking.
27. I feel annoyed when people ask me to repeat.
28. I feel embarrassed when people ask me to repeat.
29. My voice makes me feel incompetent.
30. I am ashamed of my voice problem.

Baseline score was defined as the mean of 3 VHI-10 scores before surgery (score at the time of giving consent, score at enrollment, preoperative score). Improvement in the severity of voice disorder was measured by the change from baseline in VHI-10 score at 13 weeks after surgery (the change in VHI-10 score in the clinical trial), which was chosen as the primary endpoint. The number of enrolled subjects was 21, and there were no withdrawals/dropouts. All of the 21 subjects were included in the Efficacy Set (full analysis set [FAS]). The VHI-10 scores were 30.381 (standard deviation [SD], 4.496) at baseline and 11.476 (SD, 7.494) at 13 weeks after surgery, and the change in VHI-10 score was  $-18.905$  (SD, 6.782) and its 95% confidence interval was  $-23.708$  to  $-14.102$ . Figure 4 shows the change from baseline to 13 weeks after surgery and their 95% confidence intervals. The dashed line in the figure represents the outcome of botulinum toxin type A injection in a clinical study reported in the literature (the difference before and after treatment,  $-9.6$ ).<sup>15</sup>



\* The adjusted mean at each time point and the 95% CI for the changes from baseline to 4 or 13 weeks after surgery were calculated using the Mixed-Effect Model for Repeated Measures (MMRM) with patient as a random effect based on repeated VHI-10 measurements before surgery, at 4 weeks after surgery, and at 13 weeks after surgery. Measurements were used as the response variable, and baseline and time were used as fixed effects. The Kenward-Roger method was used to adjust degrees of freedom, and a Toeplitz covariance structure was used. There were no missing data.

**Figure 4. Change from baseline in VHI-10 score at 13 weeks after surgery (FAS)**

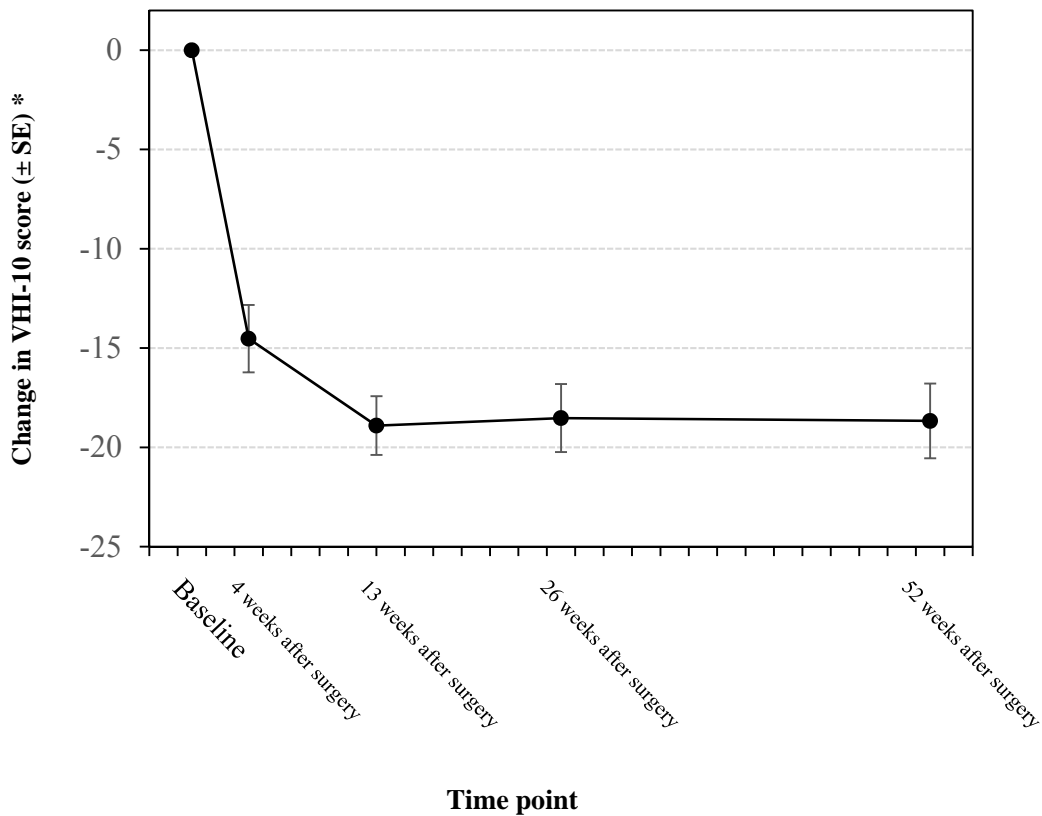
The secondary endpoints were the changes from baseline in (a) VHI-10, VHI, and VHI subscale scores, (b) phonatory function test, and (c) acoustic analysis assessment at 52 weeks after surgery.

(a) Table 9 shows changes from baseline in VHI-10, VHI, and VHI subscale scores (functional aspect [F], physical aspect [P], and emotional aspect [E]) and their standard deviations (SD) over time (up to 52 weeks after surgery). These scores decreased substantially at 4 weeks after surgery and remained low until 52 weeks after surgery. Figure 5 shows the change in VHI-10 score and its standard error (SE) over time (up to 52 weeks after surgery).

**Table 9. Changes from baseline in VHI-10, VHI, and VHI subscale scores to 52 weeks after surgery (FAS)**

Change Time point	VHI-10 (SD)	VHI (SD)	VHI subscales*		
			Functional aspect (F) (SD)	Physical aspect (P) (SD)	Emotional aspect (E) (SD)
4 weeks after surgery	-14.524 (7.780)	-43.143 (21.858)	-13.968 (8.026)	-15.429 (8.896)	-13.746 (7.098)
13 weeks after surgery	-18.905 (6.782)	-56.810 (20.616)	-17.873 (7.387)	-20.762 (7.934)	-18.175 (7.434)
26 weeks after surgery	-18.524 (7.853)	-55.762 (22.597)	-17.873 (8.226)	-19.810 (9.389)	-18.079 (7.021)
52 weeks after surgery	-18.667 (8.614)	-56.762 (23.422)	-18.635 (7.803)	-19.524 (10.008)	-18.603 (7.567)

\* Subscales consist of the functional aspect (F): questions about impairment of social life and restriction of social activities associated with voice disorder (VHI items, 1, 3, 5, 6, 8, 11, 12, 16, 19, 22), physical aspect (P): questions about self-perception of severity of voice disorder and the degree of effort to produce voice (2, 4, 10, 13, 14, 17, 18, 20, 21, 26), and emotional aspect (E): questions about anxiety and psychological stress related to voice (7, 9, 15, 23, 24, 25, 27, 28, 29, 30).



\*MMRM with the response variable of measurements and the fixed effect of time. The Kenward-Roger method was used to adjust degrees of freedom, and an unstructured covariance structure was used. There were no missing data.

**Figure 5. Change from baseline in VHI-10 score to 52 weeks after surgery (FAS)**

(b) Phonatory function test

This test was performed to assess the maximum phonation time [seconds] (the longest period during which a person can sustain phonation), the mean air flow rate [mL/sec] (expiratory volume per unit of time), vocal efficiency [%] (the ratio of the acoustic power to the aerodynamic power), and subglottic pressure [cmH<sub>2</sub>O] for the sustained vowel. Compared to the scores at enrollment, the maximum phonation score tended to increase and vocal efficiency score and subglottic pressure score slightly increased. The mean air flow rate score tended to increase at 13 and 26 weeks after surgery, but slightly decreased at 52 weeks after surgery, compared to the score at enrollment.

(c) Acoustic analysis assessment

This test was performed to assess frequency instability (jitter [%]), amplitude instability (shimmer [%]), harmonics to noise ratio (HNR [dB]), standard deviation of fundamental frequency (SDF0 [Hz]), and degree of voice breaks (DVB [%]) during sustained vowel phonation. Compared to the measurements at enrollment, jitter, shimmer, SDF0, and DVB

tended to decrease, while HNR tended to increase.

#### **6.A.(2) Safety evaluation**

Safety endpoints included (a) adverse events, (b) the incidence of malfunctions, (c) clinical laboratory tests, (d) laryngeal endoscopy, and (e) the condition of surgical wounds. All of the 21 subjects enrolled were included in the Safety Set.

##### **(a) Adverse events and (b) the incidence of malfunctions**

Adverse events occurring through 52 weeks after surgery were included in the analysis and coded to the MedDRA (Medical Dictionary for Regulatory Activities) System Organ Classes (SOCs), Preferred Terms (PTs), and Lowest Level Terms (LLTs). Fifty-one adverse event PTs were noted in 20 subjects. Adverse event PTs noted in more than one subject were procedural pain (17 subjects), viral upper respiratory tract infection (8 subjects), laryngeal haematoma (3 subjects), dermatitis contact (2 subjects), urticaria (2 subjects), and excessive granulation tissue (2 subjects). Analysis of all adverse events showed that 4 adverse events reported by 3 subjects were moderate to severe in severity (intervertebral disc protrusion, anxiety disorder, back pain, and hypertension [all moderate in severity]). There were no serious adverse events or adverse events for which a causal relationship to the investigational device could not be ruled out. The adverse events related to surgical procedure were procedural pain (17 subjects), laryngeal haematoma (3 subjects), post procedural haematoma (1 subject), hypotonia (1 subject), cough (1 subject), subcutaneous emphysema (1 subject), and excessive granulation tissue (1 subject). All adverse events are summarized in Table 10. No malfunctions occurred.

**Table 10. All adverse events occurring through 52 weeks after surgery by PT (Safety Set, N = 21)**

PT	n	Incidence (%)	PT	n	Incidence (%)
Procedural pain	17	81.0	Intervertebral disc protrusion	1	4.8
Viral upper respiratory tract infection	8	38.1	Headache	1	4.8
Laryngeal haematoma	3	14.3	Hypotonia	1	4.8
Dermatitis contact	2	9.5	Anxiety disorder	1	4.8
Urticaria	2	9.5	Dysmenorrhoea	1	4.8
Excessive granulation tissue	2	9.5	Asthma	1	4.8
Constipation	1	4.8	Cough	1	4.8
Diarrhoea	1	4.8	Rash	1	4.8
Vomiting	1	4.8	Skin exfoliation	1	4.8
Cystitis	1	4.8	Subcutaneous emphysema	1	4.8
Post procedural haematoma	1	4.8	Hypertension	1	4.8
Back pain	1	4.8			

**(c) Clinical laboratory tests**

Hematology test, clinical chemistry, and coagulation test were performed at enrollment, immediately after surgery, and at 13 weeks after surgery. Laboratory values changed immediately after surgery but were largely stable. There were no noteworthy changes associated with the clinical trial.

**(d) Laryngeal endoscopy**

During the entire follow-up period (up to 52 weeks after surgery), the investigational device did not come off or was not exposed to the airway lumen in any subject, and vocal cord mobility was present in all subjects. Examination of the appearance of the vocal cord mucosa revealed mucositis in 13 subjects and edema in 11 subjects immediately after surgery, but no subjects had mucositis or edema at 26 or 52 weeks after surgery.

**(e) The condition of surgical wounds**

Signs of infection were absent in all of the 21 subjects during the entire follow-up period. Redness of surgical wounds was present in 3 subjects immediately after surgery but was absent in all subjects at 26 and 52 weeks after surgery.



## **6.B Outline of the review conducted by PMDA**

PMDA reviewed the data by focusing on the following points and taking account of comments raised in the Expert Discussion.

- (1) Clinical significance
- (2) Appropriateness of the clinical trial
  - 1) Appropriateness of the endpoint and inclusion of a control group
  - 2) Justification for sample size
  - 3) Evaluation period
  - 4) Justification for extrapolating the results of the clinical trial with the investigational device having a different specification from TITANBRIDGE to clinical evaluation of TITANBRIDGE
- (3) Efficacy
  - 1) Clinical significance of postoperative change in VHI score from baseline
  - 2) 2 subjects without improvement in VHI-10 score
  - 3) Secondary endpoints
- (4) Safety
- (5) Provision of information regarding the use of TITANBRIDGE

### **6.B.(1) Clinical significance**

Although adductor spasmodic dysphonia is a serious and intractable disease, there is no curative treatment at present. Botulinum toxin type A injection is employed worldwide, but it is unapproved in Japan. Its low invasiveness and high response rate are known, but the duration of action is limited to 3 to 4 months. Even during that period, patients treated with injections of botulinum toxin type A may have symptoms such as swallowing and breathing difficulties. While the effectiveness of thyroarytenoid myectomy has been reported to be comparable to that of type II thyroplasty,<sup>20,21</sup> the former is a highly invasive procedure in which the thyroarytenoid muscle is excised as much as possible under general anesthesia. This surgery has been performed at only a limited number of medical institutions due to the persistence of a hoarse voice associated with vocal cord atrophy and scarring after surgery.

On the other hand, type II thyroplasty with titanium bridges is a surgical procedure in which the thyroid alae are pulled apart at the attachment of bilateral thyroarytenoid muscles and fixed permanently. The procedure is expected to have a permanent treatment effect. Moreover, this surgical procedure is less invasive than the existing surgical therapy (i.e., thyroarytenoid myectomy), and the surgeon can adjust the distance of separation of the thyroid alae while monitoring the patient's voice for improvement in hoarseness.

Based on the above points and considering that no satisfactory treatment for adductor spasmodic dysphonia has been established in Japan, making TITANBRIDGE available for use in clinical practice is meaningful as long as the clinical efficacy and safety of type II thyroplasty with titanium bridges are demonstrated.

## **6.B.(2) Appropriateness of the clinical trial**

### **6.B.(2).1 Appropriateness of the endpoint and inclusion of a control group**

The applicant's explanation about the primary efficacy endpoint for the clinical trial:

Vocal function is assessed objectively by phonatory function test (the maximum phonation time, the mean flow rate, and expiratory pressure) and acoustic analysis (e.g., pressure amplitude of vocal cord vibration) (hereinafter collectively referred to as "objective voice measurements"). However, adductor spasmodic dysphonia is characterized by involuntary and intermittent spasms of the intrinsic muscles of the larynx during phonation, which cause forceful adduction of the vocal cords and overclosure of the glottis, resulting in symptoms such as strangulation, breathiness, interruption, and tremor. Such symptoms vary from patient to patient, and the severity of the symptoms changes according to time and occasion, even in patients with persistently worsened symptoms. For these reasons, the applicant considered that the efficacy of type II thyroplasty with titanium bridges in the treatment of adductor spasmodic dysphonia could not be evaluated using objective voice measurements as the primary endpoint.

On the other hand, VHI is a 30-item questionnaire to assess voice disorders, proposed by Jacobson et al. in 1997.<sup>11</sup> It consists of 30 questions to assess patient perception of the severity of symptoms, and each question is scored from 0 to 4. The total VHI score is a tool to quantify vocal handicap. The higher total score represents more strongly self-perceived vocal handicap. The reliability and validity of VHI and VHI-10, a shorter version of VHI consisting of the major 10 questions, have been confirmed,<sup>12,14</sup> and VHI and VHI-10 are internationally established assessment scales. There is a high correlation between the two scales, and simpler VHI-10 has been used in clinical practice. On the above grounds, a subjective measure VHI-10 was chosen as the primary endpoint.

An open-label, uncontrolled trial design was chosen from the feasibility and clinical standpoints, because only a limited number of medical institutions were thought to conduct the clinical trial appropriately, and because there was no alternative treatment as a control.

PMDA's view:

Adductor spasmodic dysphonia causes a variety of symptoms and has some specific features. For example, the symptoms tend to exacerbate under stress or in a noisy environment; the severity of the symptoms changes according to occasion, even in patients with persistently worsened

symptoms; and words or sentences that are difficult to say are different among individual patients. Acoustic analysis, phonatory function test, and other objective voice measurements are performed to assess the vowel sustained for a limited time. These instruments can serve to evaluate one aspect of individual symptoms of the patient, but have difficulty in comprehensively assessing the severity of the symptoms characteristic of the disease.

On the other hand, VHI-10, which was used as the primary endpoint for the clinical trial, allows for subjective assessment of the severity of voice disorders, while it is an internationally established objective scale to assess voice disorders and its reliability and validity have been confirmed. Hence, VHI-10 is a tool suitable for the assessment of the severity of adductor spasmodic dysphonia, and it is appropriate for the applicant to evaluate the efficacy of type II thyroplasty with titanium bridges based on VHI-10.

Subjective assessment using VHI-10 may cause a bias in efficacy evaluation (i.e., patients feel as if their symptoms worsened or improved due to surgery). This is acceptable for the following reasons (a) and (b).

- (a) The true endpoint for the treatment effect of type II thyroplasty with titanium bridges is patients' perception of the effectiveness of the surgical therapy, and therefore subjective assessment is important.
- (b) The results of the secondary endpoints of objective voice measurements (e.g., phonatory function test and acoustic analysis assessment) support the results of the primary endpoint of VHI-10 on an individual patient basis.

Although a control group was not included in the clinical trial, efficacy evaluation based on the postoperative change in VHI-10 score from baseline in the clinical trial has been justified for the following reasons (a), (b), and (c).

- (a) VHI was used in 2 preceding clinical research programs at Kumamoto University and in a foreign clinical study to evaluate the effect of botulinum toxin injection. Symptom improvement measured by the VHI scores in those studies was used as reference to determine the sample size and response criteria for the clinical trial.
- (b) Patients undergoing thyroarytenoid myectomy, which is a possible alternative treatment but highly invasive, are limited. The inclusion of these patients in the clinical trial as a control group is difficult.
- (c) Adductor spasmodic dysphonia is an intractable disease unresponsive to voice therapy, and its symptoms are unlikely to improve spontaneously (without treatment).

#### **6.B.(2).2) Justification for sample size**

The applicant's justification for sample size:

Adductor spasmodic dysphonia is an intractable disease, and there is no standard of care for this disease. Based on the data from the preceding clinical research programs, the expected change in VHI-10 score at 3 months after surgery was estimated at  $-12.8$ , and its standard deviation at  $3.8$ . On the other hand, in a clinical study in which 133 patients with adductor spasmodic dysphonia received injections of botulinum toxin type A, the difference between the pretreatment and posttreatment scores for the best VHI-10 score during treatment cycles was  $-9.6$ .<sup>15</sup> Based on this result, the threshold change in VHI-10 score after type II thyroplasty with titanium bridges was determined to be  $9.6$ , and 17 patients were required to reject the null hypothesis of  $\leq 9.6$  with 90% power at a two-sided significance level of  $0.05$ . Allowing for dropouts, 20 patients to be followed up were needed to demonstrate that type II thyroplasty with titanium bridges is at least equivalent to botulinum toxin type A injection. Since adductor spasmodic dysphonia is a rare disease, the sample size of 20 was justified also from the standpoint of the number of patients that can be accrued.

PMDA's view:

There is no standard of care for adductor spasmodic dysphonia in or outside of Japan. Because botulinum toxin type A injection is employed worldwide, sample size determination based on the effect of the therapy (i.e., change in VHI score,  $-9.6$ ) is justifiable. Since TITANBRIDGE is an orphan medical device, sample size determination based on feasibility is acceptable.

### **6.B.(2).3) Evaluation period**

The applicant's explanation about the evaluation period:

In the clinical research programs using titanium bridges, 16 patients had a preoperative VHI score of  $\geq 20$ . The mean VHI-10 scores in these patients were  $28.3$  (SD,  $4.6$ ) before surgery and  $5.6$  (SD,  $4.0$ ) at 3 months after surgery, and the change was  $-22.6$  (SD,  $5.2$ ). The symptoms were stable for  $\geq 1$  year, demonstrating sustained efficacy. Thus, assessment at 13 weeks after surgery chosen as the timing of the primary endpoint and the proposed follow-up period of 52 weeks after surgery were considered appropriate.

PMDA's view:

In the preceding clinical research programs, VHI-10 score improved substantially at 4 weeks after surgery, and symptom improvement tended to be maintained for  $\geq 1$  year. Primary efficacy evaluation based on the change from baseline in VHI-10 score at 13 weeks after surgery (at the time when patients can speak normally) in the clinical trial should be appropriate.

There was no particular problem with selecting an evaluation period of 52 weeks after surgery for

other efficacy and safety endpoints. The evaluation period was determined based on long-term efficacy and safety data (up to 2 years) from the preceding clinical research programs. The data were available at the time of the clinical trial design, though the number of patients evaluated was limited.

**6.B.(2).4) Justification for extrapolating the results of the clinical trial with the investigational device having a different specification from that of TITANBRIDGE to clinical evaluation of TITANBRIDGE**

The basic specification for the investigational device (titanium bridges) used in the clinical trial was established based on experience in the preceding clinical research programs.

The applicant's explanation about the justification for extrapolating the results of the clinical trial with the investigational device to clinical evaluation of TITANBRIDGE:

Despite the differences between TITANBRIDGE and the investigational device, the data submitted can be justified for the following reasons (a), (b), and (c), described in Section "2.5.A Summary of the submitted data."

- (a) The critical region for the efficacy of TITANBRIDGE is the bridge region. As long as failure of the bridge region does not occur and the correct distance of separation is maintained, wing fractures do not necessarily lead to reduced efficacy of TITANBRIDGE.
- (b) The basic specification for the bridge region of the standard specification product is identical to that of the investigational device. Compression fatigue testing of the bridge region showed satisfactory results for all basic specification products. The maximum load at which the specimen withstood the specified number of cycles was much greater than the load resulting in an injury of the thyroid cartilage (█N). TITANBRIDGE has performance required for the bridge region for clinical use.
- (c) The shape and structure of the wing (e.g., width, thickness, inner hole shape) for each basic specification product were devised to increase fatigue strength compared to the investigational device. In addition, both TITANBRIDGE and the investigational device have durability to withstand the cyclic load applied during swallowing or other laryngeal movements, which is required for clinical use.

As described above, all basic specification products were shown to have increased strength compared to the investigational device and sufficient performance required for clinical use. Thus, there is no problem with extrapolating the results of the clinical trial with the investigational device to clinical evaluation of TITANBRIDGE.

PMDA's view:

The basic specification was reviewed before regulatory submission, and the data to support increased strength of TITANBRIDGE compared to the investigational device were submitted. The data has demonstrated that TITANBRIDGE has sufficient mechanical performance required for clinical use. As the applicant explained, the clinical efficacy and safety of type II thyroplasty with TITANBRIDGE can be evaluated based on the results of the clinical trial with the investigational device.

### **6.B.(3) Efficacy**

#### **6.B.(3).1 Clinical significance of postoperative change in VHI score from baseline**

The applicant's explanation about the clinical significance of the mean change from baseline in VHI-10 score at 13 weeks after surgery (-18.905) in the clinical trial (the primary endpoint):

The sample size for the clinical trial was determined based on the outcome of botulinum toxin type A injection in patients with adductor spasmodic dysphonia in a clinical study reported in the literature (-9.6). Since the lower limit of the 95% confidence interval for the mean change in VHI-10 score (-14.102) in the clinical trial was greater than the value obtained with botulinum toxin treatment (-9.6), the efficacy of type II thyroplasty with titanium bridges was shown to be equivalent to or greater than that of botulinum toxin type A injection.

PMDA's view about the clinical significance of improvement in VHI score:

The results of the clinical trial showed that the effect of type II thyroplasty with titanium bridges was equivalent to or greater than that of botulinum toxin type A injection in terms of improvement in VHI-10 score, demonstrating the efficacy of the former therapy. However, botulinum toxin type A injection was unapproved in Japan at the time of regulatory submission. In addition to demonstrating the efficacy, the applicant should provide a supplementary explanation about the interpretation of the change in VHI-10 score in the clinical trial to show the clinical significance of type II thyroplasty with titanium bridges.

Because there have been no data from prospective studies verifying the clinical significance of the change in VHI score, the published literature was used for discussion. The changes in VHI-10 and VHI scores (VHI was evaluated in the same manner as VHI-10) in the clinical trial, and the differences in VHI score between dysphonic patients and non-dysphonic patients or healthy volunteers reported in the literature in Japan are shown in Tables 11 to 13.

**Table 11. VHI and VHI-10 scores in the clinical trial**

Outcome measure	Before surgery (Baseline) (n = 21)			13 weeks after surgery (n = 21)			Difference (change)
	Mean score	SD	95% CI	Mean score	SD	95% CI	
VHI	87.190	15.110	79.196-95.185	30.381	22.413	22.386-38.376	56.810
VHI-10	30.381	4.496	28.334-32.428	11.476	7.494	8.065-14.887	18.905

**Table 12. VHI and VHI-10 scores in the dysphonia and healthy volunteer groups<sup>14</sup>**

Outcome measure	Dysphonia* (n = 171)			Healthy volunteers* (n = 105)			Difference**
	Mean score	SD	95% CI	Mean score	SD	95% CI	
VHI	34.1	29.6	29.6-38.6	6.7	8.5	5.1-8.4	27.4
VHI-10	12.8	10.3	11.3-14.4	3.0	3.2	2.4-3.6	9.8

\* Dysphonia group: dysphonic patients, regardless of type of disease

Healthy volunteer group: healthy adults without a history of dysphonia

\*\* Mean differences are listed as reference data.

**Table 13. VHI scores in the dysphonia and non-dysphonia groups<sup>22</sup>**

Outcome measure	Dysphonia* (n = 74)			Non-dysphonia* (n = 87)			Difference**
	Mean score	SD	95% CI	Mean score	SD	95% CI	
VHI	40.3	21.5	35.3-45.3	19.3	18.2	15.4-23.1	21

\* Dysphonia group: dysphonic patients, regardless of type of voice disease

Non-dysphonia group: non-dysphonic outpatients at general hospitals with outpatient clinics of otorhinolaryngology or dysphonia

\*\* Mean differences are listed as reference data.

According to the published literature, there were significant differences in mean VHI and VHI-10 scores between the dysphonia and healthy volunteer groups ( $t(271) = 9.23$ ,  $P < 0.001$  and  $t(273) = 9.80$ ,  $P < 0.001$ , respectively). A significant difference in mean VHI score between the dysphonia and non-dysphonia groups was observed ( $t(159) = 6.707$ ,  $P < 0.001$ ). In the literature, the between-group comparisons using VHI and VHI-10 showed clear statistically significant differences with regard to dysphonia, which were of clinical significance.

The differences (changes) in VHI and VHI-10 scores in the clinical trial were much greater than the differences in VHI and VHI-10 scores reported in the literature. However, whether type II thyroplasty with titanium bridges can be effective enough to cure dysphonia cannot be determined by simply comparing these results, because the patient groups studied in the literature were different from the population of the clinical trial.

Nevertheless, if the changes in VHI and VHI-10 scores in the clinical trial are comparable to the

differences reported in the literature, it should be appropriate to conclude that the symptoms of dysphonia have improved with clinically evident changes in vocal symptoms. Thus, the efficacy of type II thyroplasty with titanium bridges shown based on the changes in VHI and VHI-10 scores in the clinical trial, has clinical significance in terms of improvement in the symptoms of dysphonia, and the efficacy results adequately fulfill the intended use of the product presented by the applicant at regulatory submission.

**6.B.(3).2) Two subjects without improvement in VHI-10 score**

The applicant’s explanation about subjects showing a small change in VHI-10 score in the clinical trial (the changes from baseline to 13 weeks after surgery were –3.67 and –5.67):

Table 14 shows data from 2 subjects showing a small change in VHI-10 score at 13 weeks after surgery (the primary efficacy endpoint). No major changes in VHI-10 score were noted in the 2 subjects until 52 weeks after surgery.

**Table 14. Change in VHI-10 score over time after surgery**

Subject number	[REDACTED]		[REDACTED]	
	VHI-10	Change from baseline	VHI-10	Change from baseline
Baseline	32.67	-	25.67	-
4 weeks after surgery	32.0	-0.67	22.0	-3.67
13 weeks after surgery	29.0	-3.67	20.0	-5.67
26 weeks after surgery	28.0	-4.67	23.0	-2.67
52 weeks after surgery	32.0	-0.67	29.0	3.33

The reason for no improvement in VHI-10 score was considered as follows: when the thyroid cartilage was split in the midline and pulled apart, the cut edges of the thyroid cartilage were pulled apart abruptly. As a result, the anterior right vocal cord was detached from the thyroid cartilage, resulting in a reduced effectiveness of the titanium bridge used to keep the split thyroid ala apart. Postoperative phonatory function test and acoustic analysis produced variable results, depending on time point, which precluded the use of these objective measurements for assessment of the trend of worsening or improving voice quality after surgery. On the above grounds, the “Method of Use” section of the package insert will advise that the cut edges of the thyroid cartilage divided in the midline should be pulled apart gradually.



PMDA's view:

In order to ensure the effectiveness of TITANBRIDGE used to keep the split thyroid ala apart, procedural precautions taken when splitting and separating the thyroid ala should be communicated to surgeons more specifically. Hence, procedural precautions taken when splitting and separating the thyroid ala should be included also in the "Precautions for Use" section of the package insert.

The applicant agreed to include the above information in the package insert and did so appropriately. PMDA accepted it. As later described (the condition of approval), the applicant should provide training sessions etc. to surgeons who intend to use TITANBRIDGE so that the surgeons will acquire knowledge and skills required to split and separate the thyroid ala.

### **6.B.(3).3) Secondary endpoints**

The applicant's explanation:

VHI and VHI subscale scores decreased substantially at 4 weeks after surgery and remained low until 52 weeks after surgery, showing a similar trend to VHI-10 score (the primary endpoint). Phonatory function test generally shows that phonatory function as assessed by the maximum phonation time, the flow rate, and vocal efficiency, is impaired or tends to be impaired in patients with adductor spasmodic dysphonia compared to healthy adults.<sup>23</sup> In the clinical trial, there was a trend toward improvement in the maximum phonation time and slight improvement in vocal efficiency and the mean flow rate after surgery, but the results were highly variable at different time points. Subglottal pressure tended to improve at 13 to 26 weeks after surgery, but tended to return toward the preoperative value at 52 weeks after surgery. However, the applicant considered that subglottal pressure would be unaffected because the mean value at enrollment and the range of values measured after surgery in the entire patient population were also within the normal range. Acoustic analysis assessment showed that jitter, shimmer, and DVB tended to decrease and that HNR tended to increase. These results indicate decreased instability of vocal cord vibration, decreased frequency of voice breaks, and decreased noise component passing through the glottis, showing clinical improvement in voice. These objective assessments also showed a trend toward clinical improvement. These results did not contradict each other and supported the results of the primary endpoint, further verifying the efficacy of type II thyroplasty with titanium bridges.

PMDA's view:

Patients with a variety of vocal symptoms specific to adductor spasmodic dysphonia were enrolled in the clinical trial. It is difficult to evaluate the overall efficacy of type II thyroplasty with titanium bridges in 21 patients based on objective secondary endpoints (e.g., acoustic analysis and phonatory function test). However, analysis of data from individual patients showed favorable outcomes. The results of secondary endpoints suitable for assessing each patient's vocal symptoms showed a trend toward improvement, which supported the results of the primary endpoint. Thus, there was no particular problem with the secondary endpoints selected for the clinical trial to assess the effectiveness of type II thyroplasty with titanium bridges, and these secondary endpoints were appropriate.

#### **6.B.(4) Safety**

The applicant's explanation:

The most commonly observed adverse event in the clinical trial was transient procedural pain (17 subjects), which resolved within several days post-procedure. There were no adverse events for which a causal relationship to the titanium bridge could not be ruled out or serious adverse events. No serious, unknown adverse events or malfunctions posing a serious risk occurred in the clinical trial.

All the clinical laboratory values and laboratory changes noted were within the ranges expected in this therapeutic area or following surgery, and no major laboratory changes occurred postoperatively. Adverse events observed in  $\geq 2$  subjects in the clinical trial are events that may occur commonly at the surgical site or in this therapeutic area. These events were not considered unique to type II thyroplasty with titanium bridges.

Moderate to severe adverse events were not necessarily unique to type II thyroplasty with titanium bridges. Taking into account that there were no particular problems with laryngeal endoscopic observation, the condition of surgical wounds, or other examinations, overall evaluation indicates high safety of the procedure associated with type II thyroplasty with titanium bridges.

Among surgical procedure-related adverse events, excessive granulation tissue and laryngeal haematoma in the larynx were considered associated with mucosal damage in the region of the anterior commissure or unnecessary detachment of inner perichondrium. In order to reduce these adverse events, the treating surgeon should carefully split the thyroid cartilage only and avoid tissue damage around the anterior commissure. Thus, relevant information will be included in the "Precautions for Method of Use" section of the package insert. Among surgical procedure-related adverse events, hypotonia only remained unresolved at 52 weeks after surgery. Failure to divide the thyroid ala in the exact midline resulted in mild relaxation of the left vocal cord. However,

VHI-10 score in this patient improved substantially from 23.0 before surgery to 2.0 at 13 weeks after surgery, and then to 1.0 at 52 weeks after surgery. The patient's postoperative course was favorable. The applicant considered that there were no particular safety concerns.

PMDA's view

In the clinical trial, there were no titanium bridge failure or other malfunctions or adverse events possibly causally related to type II thyroplasty with titanium bridges. Information regarding surgical procedure-related adverse events and procedural precautions have appropriately been included in the package insert. PMDA discussed procedural precautions, taking also account of comments raised at the Expert Discussion. Considering that surgeons who intend to use TITANBRIDGE can acquire necessary knowledge and skills from training sessions, workshop, etc., PMDA has concluded that the provision of training to the relevant surgeons should be specified in the condition of approval (described later) to ensure that procedural precautions are communicated appropriately to the relevant surgeons.

#### **6.B.(5) Provision of information regarding use of TITANBRIDGE**

PMDA's view:

Patients eligible for the therapy with TITANBRIDGE should be selected carefully in light of the following points: (i) Patients with adductor spasmodic dysphonia receive appropriate voice training (voice therapy) prior to surgical treatment, (ii) there are similar diseases that respond to voice therapy, and (iii) the symptoms are unstable and may exacerbate shortly after onset. Precautions taken when splitting and separating the thyroid ala in type II thyroplasty include the following advice: (1) The thyroid cartilage only should be split so as not to damage tissue around the anterior commissure, and (2) the cut edges of the split thyroid ala should be pulled apart gradually to avoid detachment of the anterior commissure. Careful manipulation during type II thyroplasty is required because the vocal cords are attached near the midline of the posterior part of the thyroid cartilage. These precautions should be included in the package insert and other instructions for use and should be communicated to relevant surgeons also through workshop or on other occasions.

On the above grounds, TITANBRIDGE should be used appropriately by surgeons with adequate knowledge of adductor spasmodic dysphonia and knowledge and experience required to perform type II thyroplasty. Thus, in addition to the inclusion of necessary information in the package insert, the condition of approval (described later) should be imposed so that the applicant will take necessary measures to ensure that surgeons who intend to perform type II thyroplasty can acquire necessary knowledge and skills.

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

### **7.A Summary of the submitted data**

In addition to the clinical trial that evaluated the efficacy and safety of type II thyroplasty with titanium bridges, the long-term outcomes of the therapy were determined in a retrospective survey by Sanuki et al.<sup>24</sup> This retrospective study reported the efficacy and safety of the surgical therapy over  $\geq 36$  months after surgery (at the time of regulatory submission), but the number of patients included in the study was limited (17 patients). In the clinical trial, only 21 patients underwent type II thyroplasty with titanium bridges and were followed up for 52 weeks.

Moreover, TITANBRIDGE was developed in Japan, and there is no clinical experience with use of TITANBRIDGE overseas. There are no foreign products that can be used for similar therapy.

On the basis of the above facts, the applicant considered that the efficacy and safety of type II thyroplasty with TITANBRIDGE should be evaluated based on the post-marketing data obtained in routine clinical settings and therefore decided to conduct a use-results survey. The planned sample size is 100 patients (at  $\geq 10$  sites), the patient follow-up period is 2 years, and the planned survey period is 6 years.

Type II thyroplasty is a surgery, and basically, drug therapy or other therapies are not necessary after discharge. For this reason, patients with improved symptoms after surgery may be lost to follow-up. Thus, the dropout rate during the 2-year follow-up period of the survey was estimated at 50%. Based on the dropout rate, the planned number of patients surveyed was set at 50 patients, and the planned enrollment was set at 100 patients.

The survey items are the VHI-10 (subjective voice assessment) and the GRBAS scale<sup>25</sup> for perceptual evaluation of voice quality (overall grade, roughness, breathiness, asthenia, and strain) by clinicians (objective voice assessment). The GRBAS scale was selected for the following reasons: (i) it is a method for psychoacoustic evaluation of hoarse voices, developed by the Committee for Phonatory Function Tests of the Japan Society of Logopedics and Phoniatrics, and (ii) vocal features can be rated and the severity of hoarseness can be quantified with high reproducibility in a short period of time, without using a test instrument. Laryngeal endoscopy, adverse events, and malfunctions were included for safety evaluation.

An outline of use-results survey (draft) is shown in Table 15.

**Table 15. Outline of use-results survey (draft)**

Objective	To detect and assess safety, quality, and efficacy information over a long period of time after surgery (including malfunctions of TITANBRIDGE, health damage caused by malfunctions, and adverse events)
Planned sample size	100 patients
Survey period	6 years (preparatory period for marketing, 0.5 years; patient enrollment period, 2 years; patient follow-up period, 2 years; and analysis period, 1.5 years)
Survey items	<ul style="list-style-type: none"> <li>(1) Preoperative baseline <ul style="list-style-type: none"> <li>(a) Surgeon/patient information</li> <li>(b) Patient characteristics</li> <li>(c) Subjective voice assessment (VHI-10) and objective voice assessment (GRBAS)</li> <li>(e) Assessment of the primary disease</li> </ul> </li> <li>(2) Information on type II thyroplasty performed <ul style="list-style-type: none"> <li>(a) Product information (size, lot number)</li> <li>(b) Safety evaluation (laryngeal endoscopy)</li> <li>(c) Adverse events, malfunctions, and health damage caused by malfunctions</li> </ul> </li> <li>(3) Follow-up (at 4, 13, 26, 52, 78, and 104 weeks after surgery) <ul style="list-style-type: none"> <li>(a) Subjective voice assessment (VHI-10) and objective voice assessment (GRBAS)</li> <li>(b) Revision thyroplasty (yes/no)</li> <li>(c) Changes in patient's social environment</li> <li>(d) Withdrawal/dropout from treatment (follow-up)</li> <li>(e) Adverse events, malfunctions, and health damage caused by malfunctions</li> </ul> </li> </ul>

### **7.B Outline of the review conducted by PMDA**

PMDA's view:

Efficacy and safety evaluation should be continued in post-marketing surveillance because (i) TITANBRIDGE is an orphan medical device, (ii) the number of patients assessed in the clinical trial was limited (21 patients), and (iii) TITANBRIDGE was developed in Japan and has never been used in overseas clinical settings. It is appropriate to evaluate efficacy based on the VHI-10 score and objective voice assessment, as in the clinical trial. The GRBAS scale is used for perceptual evaluation of voice quality (for rating vocal features and quantifying the severity of hoarseness). The GRBAS scale is appropriate for evaluating the effectiveness of type II thyroplasty with TITANBRIDGE, because the distance of separation of the thyroid alae can be adjusted while checking improvement in hoarseness during the surgery.

The following points (a) and (b) were taken into consideration when determining the appropriateness of the use-results survey period.

(a) Efficacy

≥2-year data available at the time of regulatory submission included only a small number of patients; long-term follow-up patients retrospectively studied in the preceding clinical research programs and patients included in the clinical trial.

(b) Safety

Although no failures of titanium bridges were reported in the clinical trial, device failures were previously reported by a total of 12 patients in the preceding clinical research programs: wing fractures reported by 11 of 385 patients in the preceding clinical research programs and bridge fracture reported by 1 patient treated outside the preceding clinical research programs. In approximately 70% of patients with these fracture cases (8 patients), fractures were found during revision surgery performed within 2 years after the day of the initial surgery. Patients with these fracture cases (excluding the case of bridge fracture) experienced no adverse events such as tissue damage around the site of insertion, and the titanium bridges remained fixed in appropriate positions. However, the number of patients included in the clinical trial was also limited and the occurrence of device failure-related adverse events should also be considered. Patients should therefore be followed up for a certain period of time also after the product launch.

Based on the above considerations, the plan proposed by the applicant (the patient follow-up period of 2 years and the use-results survey period of 6 years) is appropriate.

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

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

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

#### **PMDA's conclusion concerning the results of the on-site GCP inspection**

The new medical device application data (6-1-1 and 6-2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

### **IV. Overall Evaluation**

TITANBRIDGE is a hinged bridge made of titanium, which is used to keep the split thyroid ala apart in type II thyroplasty for improvement in the symptoms of adductor spasmodic dysphonia. The key issues in the product review were (1) justification for extrapolating the data from the

clinical trial with the investigational device having a different specification from TITANBRIDGE to clinical evaluation of TITANBRIDGE, (2) efficacy and clinical significance, (3) post-marketing safety measures, and (4) use-results evaluation. PMDA reached conclusions on the key issues, taking account of comments raised in the Expert Discussion. The conclusions are presented in the sections below.

**(1) Justification for extrapolating the results of the clinical trial with the investigational device having a different specification from TITANBRIDGE to clinical evaluation of TITANBRIDGE**

On the basis of the overall evaluation of the following considerations (a), (b), and (c), PMDA has concluded that there is no particular problem with the strength required for TITANBRIDGE and with specification changes and that extrapolation of the data from the clinical trial with the investigational device to clinical evaluation of TITANBRIDGE is justified.

**(a) Bridge region of TITANBRIDGE**

The bridge region of TITANBRIDGE is intended to keep the split thyroid ala apart. Thus, the clinically acceptable strength required for the bridge region is determined to be  $\geq 100$  N based on the fracture strength of the thyroid cartilage. Non-clinical testing of the bridge region (static compression and compression fatigue testing) was conducted under conditions simulating clinical use, showing that all basic specification products submitted for approval have sufficient strength. TITANBRIDGE was designed to have mechanical strength equivalent (the standard specification product and the product for patients with short thyroid cartilage) to or higher (the product for patients with thick thyroid cartilage) than that of the investigational device. No malfunctions of the bridge region were observed also with the investigational device in the clinical trial.

On the other hand, an injury of the cut edges of the thyroid cartilage is inferred to occur because the strength of TITANBRIDGE is higher than that of the thyroid cartilage. However, the cyclic forces applied on the bridge region by intrinsic and extrinsic laryngeal muscles and during swallowing or other movements are obviously weaker than the fracture strength of the thyroid cartilage, and these forces are unlikely to cause an injury of the thyroid cartilage. No adverse events such as an injury of the thyroid cartilage occurred in the preceding clinical research programs or the clinical trial.

On the basis of the above, PMDA has concluded that the setting and assessment of the strength required for the bridge region of TITANBRIDGE are appropriate.

(b) Wings of TITANBRIDGE

The fracture occurred in the medial holes of the wings of the titanium bridges used in the preceding clinical research programs. A failure analysis showed the presumed cause was fatigue fracture induced by cyclic stress. In response to these events, the wing strength of TITANBRIDGE was increased compared to the investigational device. Static 3-point bending and 3-point bending fatigue tests showed that the wing strength was increased for all basic specification products submitted for approval, compared to the investigational device. The wing strength is determined by the cross-section surface of a fatigue test specimen and the strength of raw material (pure titanium). Therefore, the raw material specification for pure titanium is provided in the “Raw Material” section of the application form and the shapes and dimensions of the wings and holes and the locations of the holes are provided in the “Shape, Structure, and Principle” section. Moreover, because analysis revealed that fracture had occurred at the site bent by the surgeon to fit the thyroid cartilage of the patient, the package insert includes the following precautions for insertion of TITANBRIDGE: If the wing of TITANBRIDGE needs to be bent to fit the thyroid cartilage of the patient, then bend it gradually, do not reverse bend, and avoid hole deformation during bending.

On the basis of the above, PMDA has concluded that there is no particular problem with safety required for the wings of TITANBRIDGE.

(c) Differences in the specification between TITANBRIDGE and the investigational device

Although a marketing application for TITANBRIDGE was submitted based on the data from the clinical trial with the investigational device, the mechanical performance and safety of TITANBRIDGE are at least equivalent to those of the investigational device based on the above considerations (a) and (b). Thus, PMDA has concluded that there is no particular problem with the differences in the specification between TITANBRIDGE and the investigational device.

**(2) Efficacy and clinical significance**

Efficacy was evaluated based on the VHI-10 score in the clinical trial. Results showed improvement in the symptoms of dysphonia at 13 weeks after surgery. The effect of type II thyroplasty with titanium bridges was shown to be equivalent to or greater than that of botulinum toxin type A injection, which is a therapy employed worldwide. The effect of the therapy with titanium bridges was shown to be sustained until 52 weeks after surgery.

PMDA discussed the clinical significance of the changes in VHI and VHI-10 scores from baseline



to a time point after type II thyroplasty with titanium bridges, based on the literature comparing the dysphonia and non-dysphonia groups using the VHI and VHI-10 (data presenting clinically apparent differences between these groups). There are limitations to explaining the effect of type II thyroplasty with titanium bridges in the clinical trial based on clinical data from different populations. However, if the changes in VHI and VHI-10 scores in the clinical trial are comparable to the difference reported in the literature, it should be appropriate to conclude that such changes represent clinically evident changes in vocal symptoms. Thus, PMDA has concluded that the efficacy of type II thyroplasty with titanium bridges demonstrated by the clinical trial has the clinical significance of improving the symptoms of dysphonia and that the efficacy results fulfill the intended use presented in the application form by the applicant.

### **(3) Post-marketing safety measures**

Patients should be selected carefully for the therapy with TITANBRIDGE in light of the following points: (i) Patients with adductor spasmodic dysphonia receive appropriate voice training (voice therapy) prior to surgical treatment, (ii) there are similar diseases that respond to non-invasive therapies such as voice therapy, and (iii) the symptoms are unstable and may exacerbate shortly after onset. There are different precautions that should be taken to ensure the safety and efficacy of type II thyroplasty.

To ensure safety, the following points (a) and (b) are important.

- (a) In order to reduce adverse events in the larynx, damage to and detachment of the anterior commissure should be prevented when splitting the thyroid cartilage.
- (b) If the wing of TITANBRIDGE needs to be bent to fit the thyroid cartilage of the patient, then bend it gradually, do not reverse bend, and avoid hole deformation during bending, in order to prevent decrease in the strength of the wing.

To ensure efficacy, the cut edges of the thyroid cartilage should be pulled apart gradually to prevent detachment of the anterior commissure.

The above advise should be included in the package insert and other instructions for use from the viewpoint of the efficacy and safety of type II thyroplasty with TITANBRIDGE. In addition, the condition of approval should be imposed to ensure that the applicant provides training sessions, workshop, etc., concerning the proper use of TITANBRIDGE to surgeons who intend to use TITANBRIDGE.

The applicant should continue collecting information on patients treated in the preceding clinical research programs and the clinical trial as well as patients who will undergo type II thyroplasty with TITANBRIDGE in post-marketing settings. It is also recommended that based on the

collected information, advice for safer treatment should be provided to surgeons and other healthcare professionals.

#### **(4) Use-results evaluation**

In the clinical trial, substantial improvement in VHI-10 score was noted at 4 weeks after surgery, and primary assessment at 13 weeks after surgery showed the clinical significance of the titanium bridge. The data from the preceding clinical research programs and the clinical trial that were available at the time of regulatory submission demonstrated long-term efficacy (approximately 2 years). Thus, TITANBRIDGE is expected to have a similar treatment effect. However, given the following reasons (a) and (b), a use-results survey is necessary.

- (a) Long-term data from the preceding clinical research programs and the clinical trial are available for only a small number of patients.
- (b) Although malfunctions as detected in the preceding clinical research programs were not reported in the clinical trial, patients should be followed up for a certain period of time to ensure that malfunctions and associated adverse events are monitored after the product launch.

Thus, PMDA has concluded that the use-results survey plan proposed by the applicant (the use-results survey period is 6 years because 0.5 years are required for preparation for marketing, 2 years for patient enrollment, 2 years for patient follow-up, and 1.5 years for analysis) is appropriate.

As a result of the above review, PMDA has concluded that TITANBRIDGE may be approved for the intended use shown below, with the following condition.

#### **Intended Use**

Improvement in the symptoms of adductor spasmodic dysphonia

#### **Condition of Approval**

The applicant is required to take necessary measures (e.g., provision of training sessions) in cooperation with relevant academic societies, so that surgeons with adequate knowledge of and experience in type II thyroplasty will adequately acquire the skills to use the product and knowledge of adductor spasmodic dysphonia and then use the product in accordance with the intended use and method of use.

The product should be designated as a medical device subject to the use-results survey, and the

use-results survey period should be 6 years.

This application should be subject to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

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