June 2, 2025
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Percutaneous repair system for tricuspid valve coaptation failure
Brand Name	TriClip System
Applicant	Abbott Medical Japan LLC
Date of Application	July 30, 2024 (Application for marketing approval)

Results of Deliberation

In its meeting held on June 2, 2025, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Council.

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

The use-results survey period should be 6 years. The product should be approved with the following conditions.

Approval Conditions

1. The applicant is required to take necessary measures, such as dissemination of the guidelines for proper use prepared in cooperation with related academic societies and provision of seminars, to ensure that physicians with adequate knowledge and experience in the treatment of symptomatic severe tricuspid regurgitation acquire skills for using the product and knowledge about complications associated with the procedures and identify patients eligible for treatment and that the physicians use the product at medical institutions with a well-established system for the treatment.
2. The applicant is required to conduct a post-marketing surveillance involving all patients treated with the product until data have been accrued from a specified number of patients , to submit annual reports on the results of analyses of long-term outcomes to the Pharmaceuticals and Medical Devices Agency, and to take appropriate measures as necessary.

3. The applicant is required to submit reports on the results of analyses of long-term outcome data from participants in the clinical studies included in the present application to the Pharmaceuticals and Medical Devices Agency, and to take appropriate measures as necessary.

Review Report

May 13, 2025
Pharmaceuticals and Medical Devices Agency

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

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	To be newly created
Brand Name	TriClip System
Applicant	Abbott Medical Japan LLC
Date of Application	July 30, 2024
Reviewing Office	Office of Medical Devices I

Review Results

May 13, 2025

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	To be newly created
Brand Name	TriClip System
Applicant	Abbott Medical Japan LLC
Date of Application	July 30, 2024

Results of Review

TriClip System is a medical device designed to treat tricuspid regurgitation (TR) in patients with symptomatic severe TR by transcatheter delivery of a clip to the tricuspid valve where it grasps and coapts the tricuspid valve leaflets.

The applicant submitted non-clinical data, which consisted of data supporting the performance, stability and durability, and directions for use of the TriClip System. There was no particular problem in the data submitted.

For the clinical evaluation of the TriClip System, the applicant submitted the results of a clinical study conducted in the US, Canada, and Europe (TRILUMINATE US pivotal study [hereinafter referred to as the "US pivotal study"]) and a Japanese clinical study (Japanese Study AMJ-504 [hereinafter referred to as the "Japanese clinical study"]). As reference data, the applicant submitted the results of the TRILUMINATE Feasibility study.

The US pivotal study was conducted in patients with symptomatic severe TR whose symptoms of TR persisted despite being optimally treated with medical therapy and who were at intermediate or greater estimated risk for mortality with tricuspid valve surgery. The study consisted of a randomized cohort and a single-arm cohort.

The randomized cohort of the US pivotal study enrolled patients in whom the TriClip System was expected to reduce TR severity to moderate or less. The primary endpoint was a hierarchical composite of "all-cause death or tricuspid valve surgery, cardiac failure hospitalizations, and quality of life (QOL) improvement assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 12 months post-procedure." The win ratio of the TriClip group compared with the control group (medical therapy group) was 1.44 (95% confidence interval [CI] [1.03, 2.08], superiority P = 0.0311), showing the superiority of the TriClip System therapy over medical therapy. The percentage of subjects with TR severity reduction to moderate or less at 30 days post-procedure was 87.0% in the TriClip group and 5.4% in the control group. The TriClip group maintained the reduced TR severity at 12 months post-

procedure. The rate of freedom from major adverse events at 30 days post-procedure was 98.3% in the TriClip group.

The single-arm cohort of the US pivotal study enrolled patients in whom the TriClip was expected to reduce TR by at least 1 grade but was unlikely to reduce TR to moderate or less because of their complex tricuspid anatomies. The primary endpoint of "rate of survival through 12 months post-procedure with KCCQ score improvement of ≥10 points from baseline" was 46.2% (the lower limit of 98.75% CI, 34.3%), meeting the performance goal of 30% ($P = 0.0008$). No major adverse events occurred through 30 days post-procedure. The proportion of subjects with TR severity reduction by at least 1 grade at 30 days post-procedure was 98.9%.

The Japanese clinical study used similar inclusion and exclusion criteria to those of the randomized cohort of the US pivotal study. The primary endpoint of "rate of freedom from all-cause death or tricuspid valve surgery through 12 months post-procedure" was 100%, meeting the performance goal (62%). The additional primary endpoint of "annualized event rate for cardiac failure hospitalizations at 12 months post-procedure" was 0.03 (events per subject-year), meeting the performance goal (0.6). A secondary endpoint, "proportion of subjects with KCCQ score improvement of ≥15 points at 12 months post-procedure," was 22.2% (8 of 36 subjects), not meeting the performance goal (35%). The rate of freedom from major adverse events through 30 days post-procedure was 100%. The proportion of subjects with TR severity reduction to moderate or less was 80%. The reduced TR severity was maintained at 12 months post-procedure.

The randomized cohort of the US pivotal study achieved the primary endpoint, to which QOL improvement mainly contributed. There was no difference in the hard endpoints, including mortality, between the TriClip and control groups. The results did not show that the TriClip System reduced TR severity to improve the prognosis of subjects. Currently, however, no effective therapy is available for patients with symptomatic severe TR despite being optimally treated with medical therapy for whom tricuspid valve surgery is not optimal. Taking into consideration the safety results and the comments from the Expert Discussion, PMDA concluded that the risk-benefit balance of the TriClip System could be ensured by selecting eligible patients.

The single-arm cohort of the US pivotal study included patients with more complex tricuspid anatomy and more progressed disease conditions than those of the randomized cohort. Nevertheless, the results in the single-arm cohort showed no concerns about the procedural safety, but improvements in QOL and symptoms were comparable to those in the randomized cohort. On the basis of these findings, PMDA concluded that the TriClip System was of clinical significance.

The TriClip System will be the first transcatheter device for the treatment of symptomatic severe TR in Japan. To ensure the effective and safe use of the TriClip System in Japan, users must acquire knowledge and skills required for the procedures of the TriClip therapy through training programs, etc., and a multidisciplinary heart team must determine whether the patient should be treated with a conventional therapy (medical or surgical therapy) or the TriClip therapy, based on a thorough understanding of the characteristics of the TriClip therapy. In addition, complications associated with the use of the TriClip

System or the placement procedures must be treated appropriately. To treat patients with symptomatic severe TR, the TriClip System should be used by physicians with sufficient experience in medical and surgical treatment of symptomatic severe TR and capability of appropriately treating such complications at medical institutions with a well-established system for the treatment.

Information regarding the procedural success rate, incidence of adverse events, and efficacy should be collected after the launch of the TriClip System in Japan through a post-marketing surveillance, etc., and additional risk reduction measures should also be taken as necessary. Because only limited knowledge about long-term outcomes of the TriClip System, including overseas data, is available, PMDA requested the applicant to submit annual reports on the clinical studies submitted in the present application, to evaluate long-term outcomes.

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

Intended Use

The TriClip System is indicated to treat tricuspid regurgitation in patients with symptomatic severe tricuspid regurgitation whose severity and symptoms persist despite optimal medical therapy and who are meet all of the following criteria, as determined by a heart team:

- Patients whose left heart disease has been adequately treated in accordance with the Japanese guidelines
- Patients for whom tricuspid valve surgery is not optimal
- Patients in whom transcatheter edge-to-edge tricuspid valvuloplasty is clinically appropriate

Approval Conditions

1. The applicant is required to take necessary measures, such as dissemination of the guidelines for proper use prepared in cooperation with related academic societies and provision of seminars, to ensure that physicians with adequate knowledge and experience in the treatment of symptomatic severe tricuspid regurgitation acquire skills for using the product and knowledge about complications associated with the procedures and identify patients eligible for treatment and that the physicians use the product at medical institutions with a well-established system for the treatment.
2. The applicant is required to conduct a post-marketing surveillance involving all patients treated with the product until data have been accrued from a specified number of patients, to submit annual reports on the results of analyses of long-term outcomes to the Pharmaceuticals and Medical Devices Agency, and to take appropriate measures as necessary.
3. The applicant is required to submit reports on the results of analyses of long-term outcome data from participants in the clinical studies included in the present application to the Pharmaceuticals and Medical Devices Agency, and to take appropriate measures as necessary.

Review Report

May 13, 2025

Product for Review

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	To be newly created
Brand Name	TriClip System
Applicant	Abbott Medical Japan LLC
Date of Application	July 30, 2024
Proposed Intended Use	The TriClip System is intended to be used to improve QOL and function in patients with symptomatic severe tricuspid regurgitation whose severity and symptoms persist despite optimal medical therapy and who meet all of the following criteria as determined by a heart team: • Patients for whom tricuspid valve surgery is not optimal • Patients in whom transcatheter edge-to-edge tricuspid valvuloplasty is clinically appropriate

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List of Abbreviations

ACE	Angiotensin Converting Enzyme
AE	Adverse Event
ALT	Alanine aminotransferase
ARB	Angiotensin Receptor Blocker
AST	Aspartate aminotransferase
BARC	Bleeding Academic Research Consortium
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Grafting
CDS	Clip Delivery System
CEC	Clinical Events Committee
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy Defibrillator
CT	Computed Tomography
eGFR	estimated Glomerular Filtration Rate
EC	Eligibility Committee
ECL	Echocardiography Core Laboratory
EROA	Effective Regurgitant Orifice Area
GGT	γ-Glutamyl Transferase
ICD	Implantable Cardioverter Defibrillator
IEC	International Electrotechnical Commission
INR	International Normalized Ratio
ISO	International Organization for Standardization
JB-POT	Japanese Board of Perioperative Transesophageal Echocardiography
jRCT	Japan Registry of Clinical Trials
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVOT	Left Ventricular Outflow Tract
MAE	Major Adverse Events
MELD-XI	Model for End-Stage Liver Disease Excluding INR
MR	Mitral Regurgitation
MRI	Magnetic Resonance Imaging
M-TEER	Mitral Transcatheter Edge-to-Edge Repair
NCT	National Clinical Trials
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PISA	Proximal Isovelocity Surface Area
QOL	Quality of Life
RVEDV	Right Ventricular End-Diastolic Volume
RVESV	Right Ventricular End-Systolic Volume
SAE	Serious Adverse Event
SGC	Steerable Guide Catheter
SHD	Structural Heart Disease
SLDA	Single Leaflet Device Attachment
sPAP	systolic Pulmonary Artery Pressure
TAPSE	Tricuspid Annular Plane Systolic Excursion
TEE	Transesophageal Echocardiogram
TR	Tricuspid Regurgitation
TTE	Transthoracic Echocardiogram
VARC	Valve Academic Research Consortium

I. Product Overview

TriClip System (herein after referred to as TriClip) consists of a Clip Delivery System (CDS) with a clip that grasps the tricuspid valve leaflets with coaptation defects, a Steerable Guide Catheter (SGC) that delivers the CDS into the right atrium, a dilator, and accessories (e.g., stabilizer, lift, and support plate) that support placement of the devices (Figure 1). The clips of the TriClip come in 4 sizes (NT, NTW, XT, and XTW) (Figure 2).

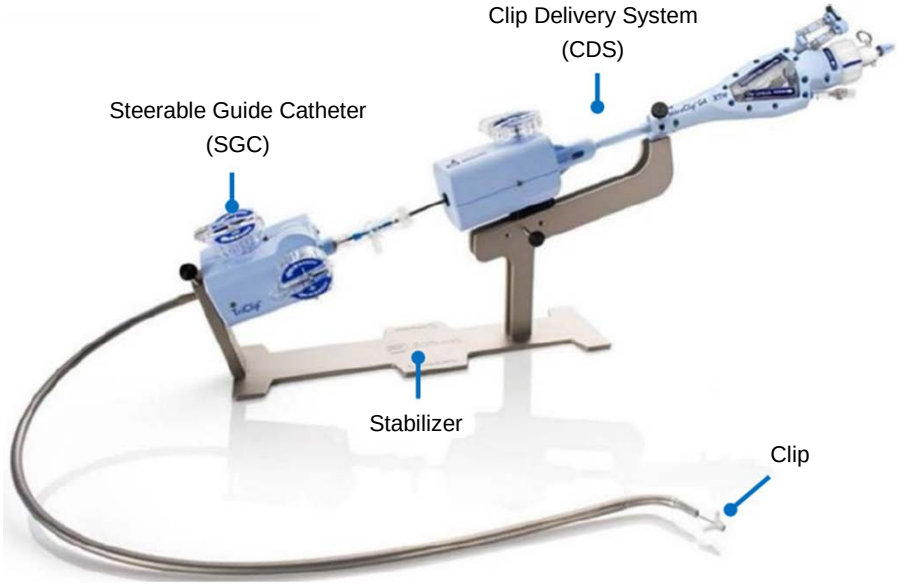


Figure 1. Exterior appearance of main constituent parts of the TriClip

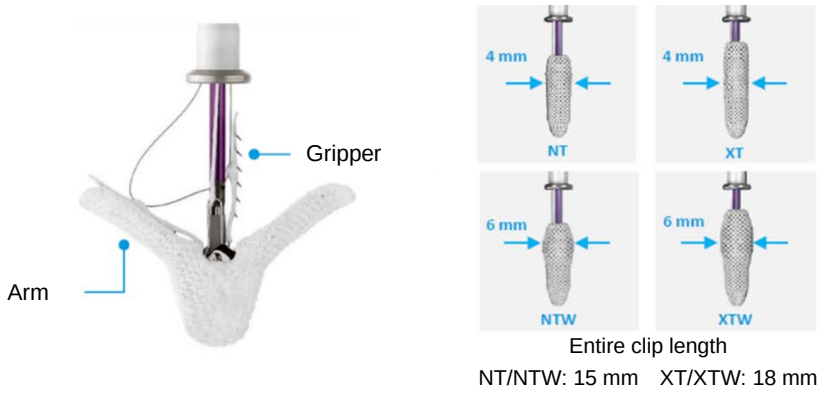


Figure 2. Exterior appearance and available sizes of the clip

The TriClip is intended to reduce tricuspid regurgitation by delivering a clip, which is connected to the CDS, to the tricuspid valve through the SGC, which is inserted from the femoral vein to the right atrium. The clip is designed to grasp and coapt the anterior, septal, or posterior leaflets (Figure 3).

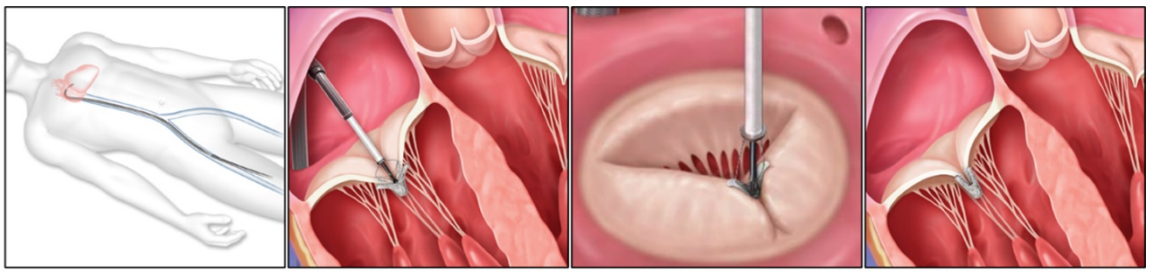


Figure 3. Placement of the TriClip device on the tricuspid valve leaflets

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

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

The expert advisors present during the Expert Discussion on the TriClip declared that they did not fall under the Item 5, Chapter 3 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.A Summary of the data submitted

1.A.(1) History of development

Tricuspid regurgitation (TR) is a disease where the tricuspid valve fails to close properly during systole, causing blood to leak backward from the right ventricle into the right atrium. Symptoms of TR include ascites, peripheral edema, hepatomegaly, loss of appetite, jugular venous distention, and abdominal distension.[1] TR has the same etiology as that of mitral regurgitation (MR). TR can be classified as organic TR (primary TR), which is caused by anatomical factors of the valve structure itself, or functional TR (secondary TR), which is associated with the pathological enlargement of the right ventricle or atrium. Secondary TR accounts for the majority of TR cases.[2,3] It is typically accompanied by pulmonary hypertension, left heart disease, right ventricular dysfunction, or atrial fibrillation.

Multiple studies have shown that the severity of TR is correlated with a decreased survival rate, regardless of left ventricular ejection fraction, pulmonary arterial pressure, or other risk factors.[2,4] Japanese and foreign guidelines recommend medical therapy (e.g., diuretics) to reduce fluid retention. Management of severe TR is, however, challenging with limited treatment options. Patients require repeated hospitalization, with poor clinical outcomes and a high 1-year mortality rate.[5,6,7] The Japanese and foreign guidelines also recommend tricuspid valve surgery as a Class I recommendation in patients with severe TR when it is performed in combination with left-sided heart valve surgery.[8,9,10] A research report shows that tricuspid valve surgery alone is associated with a high in-hospital mortality rate.[11] There is no sufficient consensus on the eligibility criteria for and optimal timing of surgery for severe TR not requiring left-sided heart valve surgery or present after heart surgery. Currently, therefore, the standard of care for severe TR not requiring left-sided heart valve surgery or present after heart surgery

is still medical therapy. There is a need for new treatment options that improve the clinical outcomes of these patients.

The TriClip has the same basic design as that of the approved product MitraClip NT System (hereinafter referred to as the MitraClip, Approval No. 22900BZX00358000) intended to treat MR, with modifications to improve the delivery to the tricuspid valve and operability. The TriClip has the same clip as that of the MitraClip. Table 1 presents the history of design changes of the TriClip.

Table 1. History of major changes

Constituent part	First generation	Second generation ([redacted])	TriClip (TriClip G4 System)
CDS	[redacted]	[redacted]	TCDS03 Clips: NT, XT, NTW, and XTW
SGC	[redacted]	[redacted]	TSGC02
Outline of changes	-	[redacted]	[redacted]

1.A.(2) Use in foreign countries

Table 2 presents the approval or clearance status of the TriClip in major foreign countries or regions (survey period, May 2022 to January 2025).

Table 2. Use in key foreign countries

Country or region	Date of approval	Intended use	Sales performance
US	April 2024	The TriClip System is indicated for improving quality of life and functional status in patients with symptomatic severe tricuspid regurgitation despite optimal medical therapy who are at intermediate or greater risk for surgery and in whom transcatheter edge-to-edge tricuspid valve repair is clinically appropriate and expected to reduce tricuspid regurgitation severity to moderate or less, as determined by a multidisciplinary heart team.	[redacted]
Europe	February 2021	The TriClip System is indicated for tricuspid valve repair to treat tricuspid regurgitation by clipping the tricuspid valve tissue.	[redacted]
Other countries	-	-	[redacted]

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

Tables 3 to 5 present common malfunctions and adverse events (incidence ≥0.1%) reported for the TriClip in foreign countries (survey period, May 2022 to January 2025).

Table 3. Malfunctions reported in foreign countries (CDS)

Malfunction	Number of events	Incidence
Incomplete coaptation (single leaflet device attachment [SLDA])	[redacted]	1.10%
Difficulty in clip opening/closing	[redacted]	0.36%
Positioning difficulty	[redacted]	0.30%
Unintended device movements	[redacted]	0.24%
Damage caused by other device	[redacted]	0.24%
Device resistance	[redacted]	0.22%
Device dislocation	[redacted]	0.17%
Removal difficulty	[redacted]	0.14%
Positioning failure	[redacted]	0.12%

Table 4. Malfunctions reported in foreign countries (SGC)

Malfunction	Number of events	Incidence
Leakage	[redacted]	0.14%

Table 5. Adverse events reported in foreign countries (CDS)

Adverse event	Number of events	Incidence
Unplanned non-surgical intervention	[redacted]	1.00%
Tricuspid regurgitation	[redacted]	0.58%
Serious injury, illness, or disability	[redacted]	0.43%
Tissue injury	[redacted]	0.36%
Hospitalization or prolonged hospitalization	[redacted]	0.22%

1.B Outline of the review conducted by PMDA

PMDA asked the applicant to explain whether any of these malfunctions and adverse events reported in foreign countries were specific to the TriClip and more commonly occurred with the TriClip procedure than with the MitraClip procedure, which is intended for use in the mitral valve, but not in the tricuspid valve.

The applicant explained that neither malfunctions nor adverse events that were specific to the TriClip or more commonly occurred with the TriClip procedure than with the MitraClip procedure were reported, and that no risk reduction measures were taken to address the malfunctions or adverse events reported in foreign countries.

PMDA accepted the applicant's explanation. The above data are discussed later in Section 6.

2. Design and Development

2.(1) Performance and safety specifications

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

The proposed performance and safety specifications for the CDS of the TriClip are clip performance, delivery system performance, steerable sleeve performance, clip introducer performance, tensile strength, torque strength, compression strength, hydrophilic coating, hemostasis valve, visibility, magnetic resonance imaging (MRI) compatibility, corrosion resistance, fatigue resistance, and flush of the delivery catheter.

The proposed performance and safety specifications for the SGC are SGC performance [redacted], tensile strength, torque strength,

hydrophilic coating, SGC hemostasis valve, and visibility. The proposed performance and safety specifications for the dilator are tensile strength and visibility.

The proposed specifications common to the whole system are biological safety, sterility assurance, ethylene oxide sterilization residuals, and bacterial endotoxins.

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

PMDA reviewed the data on the proposed performance and safety specifications for the appropriateness of the tests, methods, and specification limits, and concluded that there was no particular problem.

2.(2) Biological safety

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

The biological safety of the TriClip was evaluated in accordance with the "Revision of Basic Principles of Biological Safety Evaluation Required for Application for Market Approval of Medical Devices" (PSEHB/MDED Notification No. 0106-1, dated January 6, 2020) and the International Organization for Standardization (ISO)10993-1:2018. The applicant explained that no new study was required to assure the biological safety of the TriClip because the blood/body fluid-contacting raw materials of the TriClip, as well as the sites and duration of contacts, and sterilization method are the same as those of the MitraClip.

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

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

2.(3) Stability and durability

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

The applicant omitted the submission of stability data of the TriClip and submitted a self-declaration that the shelf life of the TriClip was determined based on the results of necessary stability evaluation, in accordance with the "Handling of Stability Studies Related to the Determination of the Shelf Life in the Application for Marketing Approvals (Certifications) of Medical Devices (in Japanese)" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012).

The applicant also omitted the submission of the study data on durability of the clip of the TriClip, which is the same as that of the MitraClip, for the following reasons.

[redacted]. This suggests [redacted]. Since the MitraClip has been shown to have fatigue resistance for [redacted], the TriClip, which is intended for use in the tricuspid valve, is expected to have fatigue resistance for [redacted].

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

PMDA reviewed the data on the stability and durability, and concluded that there was no particular problem.

2.(4) Tests supporting performance

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

The applicant submitted the data from design verification and animal studies to support the performance of the TriClip.

2.(4).A.1) Design verification studies

The CDS was tested for clip performance, delivery system performance, steerable sleeve performance, clip introducer performance, tensile strength, torque strength, compression strength, hydrophilic coating, hemostasis valve, MRI compatibility, and flush of the delivery catheter. The SGC and dilator were tested for SGC performance, tensile strength, torque strength, hydrophilic coating, and hemostasis valve. Some tests were performed using [redacted] or [redacted] as test samples. The applicant explained that they were appropriate as test samples because their parts that might affect test results are the same as those of the TriClip. The tests showed that all of the test samples met the specifications, which assures the performance of the TriClip.

The visibility of the CDS and SGC, and corrosion resistance of the CDS were evaluated based on the consistency of the raw materials of their parts and those of the MitraClip. Tests using the TriClip were omitted.

2.(4).A.2) Animal studies

To evaluate the safety and operability of the TriClip, the following 2 studies were conducted.

(a) *In vivo* animal study

This study was conducted in 15 pigs to evaluate the safety of the clip. Gross observation and histological evaluation were performed in 6 animals each (12 in total) at 30 days (±2 days) and 90 days (±2 days) after the tricuspid valve leaflets were coapted with the clip. No clinically significant gross or histological findings were observed in any animal. The clips implanted showed stable and normal movements.

One of 3 animals excluded from the study was euthanized during the procedure because the femoral vein was cut during the insertion of the delivery system and could not be repaired. One of the remaining 2 animals became weak at 25 days post-procedure and died at 37 days post-procedure. The remaining 1 animal had loss of appetite at 11 days post-procedure and was euthanized at 15 days post-procedure because echography showed no movement of the left ventricular lateral free wall or cardiac apex, but revealed pericardial thickening, ascites, and hepatic venous congestion. Although the definite causes of the deterioration of these 2 animals remain unknown, pathological examination suggests the high probability of hepatic failure, which was probably a complication associated with thoracotomy performed for epicardial echography to adjust the placement position of the clip. The event was considered not related to the TriClip.

(b) Effect on leaflet tissue and visibility of the gripper

To assess the effect on the leaflet tissue and the visibility of the gripper under echography, a test was conducted using [redacted] model ([redacted]). [redacted] were used to [redacted] in [redacted]. The test showed that the acceptance criteria [redacted] were met. It was also shown that [redacted]. After these tests, [redacted] was assessed.

All of the test samples met the acceptance criteria. Necropsy revealed only a few slight abnormalities.

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

PMDA reviewed the data on the design verification and animal studies, and concluded that there was no particular problem.

2.(5) Usability

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

The applicant submitted data supporting the conformity of the TriClip to the international standards specifying the usability engineering process of medical devices (International Electrotechnical Commission [IEC] 62366-1:2015+A1:2020).

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

PMDA reviewed the data on the conformity to IEC 62366-1, and concluded that there was no particular problem.

2.(6) Tests supporting the directions for use

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

To support the directions for use of the TriClip, the applicant submitted the results of a delivery performance test using [redacted] model. The test demonstrated that [redacted].

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

PMDA reviewed the data on the directions for use, and concluded that there was no particular problem.

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

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that the TriClip meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with

Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Public Notice No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the TriClip to the Essential Principles.

(1) PMDA's view on the conformity of the TriClip to Article 1, which stipulates preconditions, etc. for designing medical devices (particularly requirements for users, such as the expected level of technical knowledge and experience, and the expected level of education and training for users):
As described later in Section "6.B Outline of the review conducted by PMDA," provision of user training, selection of eligible patients in accordance with the guidelines for proper use prepared in corporation with the related academic societies, and compliance with the requirements for medical institutions and treating physicians are important to maintain a risk-benefit balance of the TriClip. To this end, an approval condition will be imposed to ensure that necessary measures are taken.

(2) PMDA's view on the conformity of the TriClip to Article 2, which stipulates requirements for risk management throughout the product life cycle of medical devices:
As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," the efficacy and safety of the TriClip should be evaluated in clinical practice in Japan because the clinical efficacy and safety data of the TriClip are limited. At the same time, additional risk reduction measures should be taken as necessary. PMDA instructed the applicant to conduct a post-marketing surveillance.

(3) PMDA's view on the conformity of the TriClip to Article 3, which stipulates requirements for the performance and functions of medical devices, and to Article 6, which stipulates the efficacy of medical devices:
As described later in Section "6.B Outline of the review conducted by PMDA," the results of the clinical studies submitted demonstrated that selection of eligible patients by physicians with a through understanding of the characteristics of the TriClip could ensure the efficacy and safety of the TriClip. Accordingly, the TriClip conforms to Articles 3 and 6.

(4) PMDA's view on the conformity of the TriClip to Article 17, which stipulates requirements for publicizing information including precautionary advice or the communication of information to users via instructions for use, etc. (hereinafter referred to as the "Information on Precautions etc."):
As described later in Section "6.B Outline of the review conducted by PMDA," physicians with adequate knowledge and experience in the treatment of symptomatic severe TR must select eligible patients for the TriClip therapy and users must use the TriClip after fully understanding its characteristics to maintain its risk-benefit balance. To this end, information should be provided to healthcare professionals through the Information on Precautions, etc., the guidelines for proper use, training programs, and other measures.

PMDA reviewed the conformity of the TriClip to the Essential Principles as shown above and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management, the risk management system, and its progress in accordance with ISO 14971:2019 “Medical devices—Application of risk management to medical devices.”

4.B Outline of the review conducted by PMDA

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

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on the sterilization process for the TriClip (sterilization validation, ethylene oxide sterilization residuals, and bacterial endotoxins).

5.B Outline of the review conducted by PMDA

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

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

6.A Summary of the data submitted

The applicant submitted the results of a foreign clinical study “TRILUMINATE US pivotal study” (the US pivotal study) and a Japanese clinical study “Japanese Study AMJ-504” (the Japanese clinical study) as the clinical data to evaluate the efficacy and safety of the TriClip. The US pivotal study consisted of a Roll-in cohort, a randomized cohort, and a single-arm cohort. The randomized cohort enrolled a total of 572 subjects for assignment to the TriClip group and the medical therapy group (control group). The primary analysis (hypothesis verification) was performed using data from the first 350 subjects included in the randomized cohort (175 subjects in the TriClip group, 175 subjects in the control group). The single-arm cohort enrolled 188 subjects. The primary analysis was performed using data from the first 100 subjects included in the single-arm cohort. The Japanese clinical study was conducted to assess the extrapolability of the results of the US pivotal study into the Japanese population. The study enrolled 56 subjects (19 subjects included in the Roll-in cohort, 37 subjects included in the primary analysis).

As reference data, the applicant submitted the results of the primary analysis, 2-year results in the full cohort, the results of biomarker tests, and the results of an imaging sub-study in the US pivotal study, as well as the 3-year results of the TRILUMINATE Feasibility study (the Feasibility study).

Table 6 presents a list of the results of the clinical studies submitted.

Table 6. Results of the clinical studies submitted

Study	Country /region	Sample size	Follow-up period	Submitted data
US pivotal study (primary analysis)	US Canada Europe	Roll-in cohort • TriClip group, 135 subjects Randomized cohort Primary analysis, 350 subjects • TriClip group, 175 subjects • Control group, 175 subjects Single-arm cohort Primary analysis: TriClip group, 100 subjects	5 years	1-year results: Attached document 2-year results: Reference data
US pivotal study (overall)	US Canada Europe	Full randomized cohort 572 subjects • TriClip group, 285 subjects • Control group, 287 subjects Full single-arm cohort • TriClip group, 188 subjects	5 years	2-year results: Reference data
US pivotal study Biomarker tests	US Canada Europe	• TriClip group, 285 subjects • Control group, 287 subjects	-	Reference data
US pivotal study Imaging sub-study	US Canada Europe	• TriClip group, 31 subjects • Control group, 38 subjects	-	Reference data
Japanese clinical study	Japan	Roll-in • TriClip group, 19 subjects Primary analysis • TriClip group, 37 subjects	5 years	1-year results: Attached document
Feasibility study	Europe US	• TriClip group, 85 subjects	3 years	3-year results: Reference data

6.A.(1) US pivotal study (National Clinical Trials [NCT] No. NCT03904147, study period, [redacted])

Table 7 presents a summary of the US pivotal study.

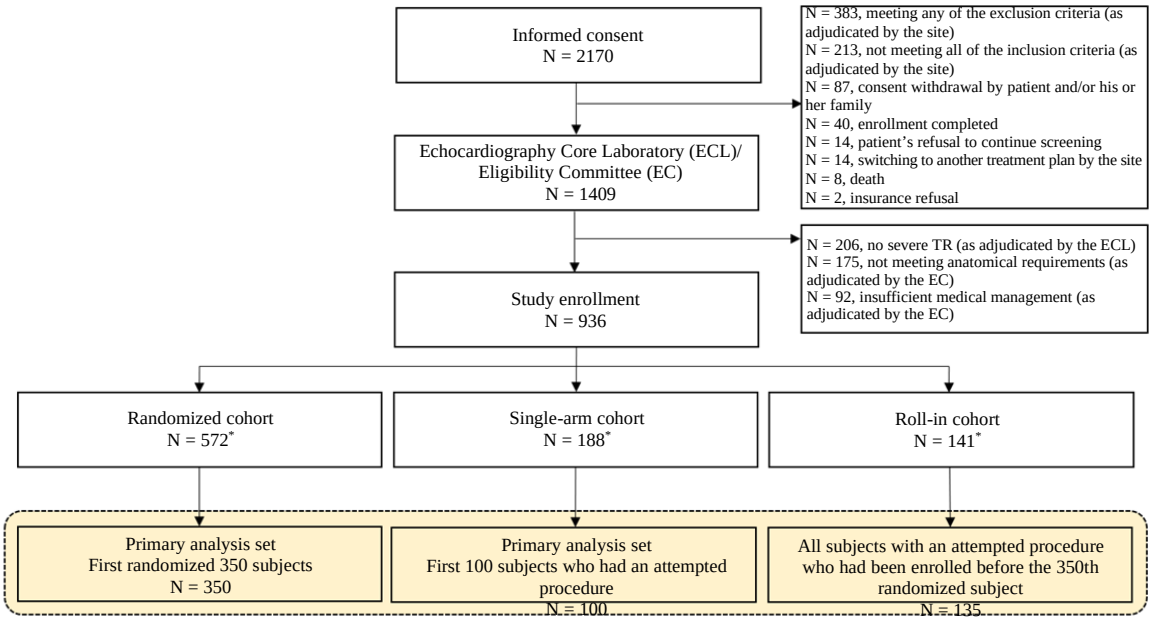
Table 7. Summary of the US pivotal study

Item	Summary
Study objective	To evaluate the efficacy and safety of the TriClip in patients with symptomatic severe TR who were at intermediate or greater estimated risk for mortality with tricuspid valve surgery as determined by site heart teams
Study design	This study was a prospective, multi-center study consisting of a Roll-in cohort, a randomized cohort, and a single-arm cohort.
Sample size	• Roll-in cohort: 135 subjects • Randomized cohort (subjects randomized at 1:1): 572 subjects (of whom, 350 were included in the primary analysis set) • Single-arm cohort: 188 subjects (of whom, 100 were included in the primary analysis set)
Key inclusion criteria	1. In the judgment of the site heart team, the patient has been adequately treated by any of the following therapies (including medical management) and stable for at least 30 days: • Optimized medical therapy for treatment of TR (e.g. diuretics) • Medical therapy or device therapy, for MR, atrial fibrillation, coronary artery disease, and cardiac failure 2. Patient has symptomatic severe TR despite being optimally treated as shown in Inclusion criterion 1. 3. Patient is at intermediate or greater estimated risk for mortality with tricuspid valve surgery as determined by a site heart team. 4. NYHA functional class (NYHA Class) II, III, or ambulatory class IV 5. In the judgment of the TriClip implanting investigator or sub-investigator, femoral vein access is possible and can accommodate a 25 Fr catheter.
Key exclusion criteria	1. Systolic pulmonary artery pressure >70 mmHg as determined by echocardiography or fixed pre-capillary pulmonary hypertension as assessed by right heart catheterization 2. Severe uncontrolled hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg) 3. Any prior tricuspid valve surgery that would interfere with placement of the TriClip device 4. Indication for left-sided heart intervention (e.g., for severe aortic stenosis and severe MR) or pulmonary valve correction within prior 60 days 5. Pacemaker or ICD leads that would prevent appropriate placement of the TriClip device 6. Tricuspid valve stenosis (defined as a tricuspid valve orifice area of ≤1.0 cm^2 or mean pressure gradient of ≥5 mmHg) 7. Left ventricular ejection fraction ≤20% 8. The following tricuspid valve leaflet anatomical characteristics which may preclude clip implantation, proper clip positioning on the leaflets, or sufficient reduction in TR; a. Evidence of calcification in the grasping area b. Presence of a severe coaptation defect (>2 cm) of the tricuspid leaflets c. Severe leaflet defect preventing proper TriClip device placement d. Epstein's anomaly (identified by having a normal annulus position while the valve leaflets are attached to the walls and septum of the right ventricle) 9. Tricuspid valve anatomy not evaluable by TTE and TEE 10. Active endocarditis, active rheumatic heart disease, or leaflets degenerated from rheumatic disease (i.e., noncompliant, perforated) 11. Myocardial infarction or known unstable angina within prior 30 days 12. Percutaneous coronary intervention (PCI) within prior 30 days 13. Hemodynamic instability (defined as systolic blood pressure <90 mmHg with or without afterload reduction, cardiogenic shock, or the need for inotropic support, intra-aortic balloon pump, or other hemodynamic support device) 14. Cerebrovascular accident within prior 90 days 15. Chronic dialysis 16. Bleeding disorders or hypercoagulable state 17. Active peptic ulcer or active gastrointestinal bleeding 18. Contraindication, allergy, or hypersensitivity to dual antiplatelet and anticoagulant therapy 19. Ongoing infection requiring current antibiotic therapy 20. Known allergy or hypersensitivity to any material of the TriClip 21. Evidence of intracardiac, inferior vena cava, or femoral venous mass, thrombus, or vegetation 22. Life expectancy of <12 months

Patient enrollment flow	Patient's eligibility determination flow Patients who met all of the inclusion and none of the exclusion criteria at each site were assessed for the severity of TR by the Echocardiography Core Laboratory (ECL) based on their echocardiogram. Subsequently, patients who had prior optimized treatment and met the anatomical requirements for the tricuspid valve as adjudicated by the Eligibility Committee (EC) were allocated to the randomized cohort or the single-arm cohort. Randomized cohort Subjects in whom the TriClip was expected to achieve TR severity reduction to moderate or less were randomized to the TriClip group or the control group at a ratio of 1:1. The primary endpoint in this cohort was evaluated when the first 350 subjects randomized to the cohort completed the 12-month follow-up. Single-arm cohort Subjects in whom the TriClip was expected to achieve TR severity reduction by ≥1 grade (as determined using a 5-point rating scale[14]) but not to moderate or less (Grade ≤2) were allocated to this cohort. All subjects were treated with the TriClip procedure. The primary endpoint in this cohort was evaluated when the first 100 subjects completed the 12-month follow-up. Each treating physician who had no experience with the TriClip procedure was allowed to treat up to 3 Roll-in subjects before the start of patient enrollment in the randomized cohort or the single-arm cohort. Deaths, cardiac failure hospitalizations, major adverse events[a] (MAEs), and other events were adjudicated by an independent Clinical Events Committee (CEC). All echocardiographic parameters were adjudicated by the ECL.
Primary endpoints	Randomized cohort The primary endpoint was a hierarchical composite of all-cause death or tricuspid valve surgery, cardiac failure hospitalizations, and quality of life (QOL) improvement assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 12 months post-procedure. The primary endpoint in the TriClip group was compared with that in the control group in the following hierarchical order: a. Time to all-cause death or tricuspid valve surgery b. Number of cardiac failure hospitalizations c. KCCQ score improvement of ≥15 points compared with baseline Single-arm cohort The primary endpoint was the rate of survival through 12 months post-procedure with a KCCQ score improvement of ≥10 points from baseline.
Secondary endpoints	Randomized cohort • The freedom from MAEs at 30 days post-procedure (femoral venipuncture) • Change in KCCQ score at 12 months post-procedure • The percentage of subjects with TR severity reduction to moderate or less at 30 days post-procedure • Change in 6-minute walk distance at 12 months post-procedure • Cardiac failure re-hospitalization at 24 months post-procedure • The freedom from all-cause death, tricuspid valve surgery, or percutaneous tricuspid valve intervention at 24 months post-procedure Single-arm cohort • TR reduction of ≥1 grade from baseline at 30 days post-procedure • The freedom from MAEs at 30 days post-procedure (femoral venipuncture) • Change in 6-minute walk distance from baseline to 12 months post-procedure • Recurrent cardiac failure hospitalization through 12 months post-procedure compared with 12 months pre-procedure • The freedom from all-cause death or tricuspid valve surgery at 12 months post-procedure
Follow-up period	5 years

[a] Definition of major adverse events (MAEs): A composite of cardiovascular death, new onset of renal failure, endocarditis requiring surgery, and non-elective cardiovascular surgery for post-procedure device-related adverse events (AEs)

Figure 4 presents the disposition of subjects enrolled in the US pivotal study.



*A total of 589 subjects were allocated to the randomized cohort (17 dropouts prior to randomization). A total of 200 subjects were allocated to the single-arm cohort (12 dropouts prior to the procedure). A total of 147 subjects were allocated to the Roll-in cohort (6 dropouts prior to the procedure).

Figure 4. Disposition of the subjects enrolled in the US pivotal study

6.A.(1).1) Randomized cohort of the US pivotal study

6.A.(1).1).(a) Randomized cohort of the US pivotal study (Primary analysis set, N = 350), 1-year results

A total of 350 subjects in whom TriClip was expected to achieve TR severity reduction to moderate or less as determined by the Eligibility Committee (EC) (175 in the TriClip group, 175 in the control group) were allocated to the randomized cohort. Figure 5 presents the follow-up status through 12 months post-procedure.

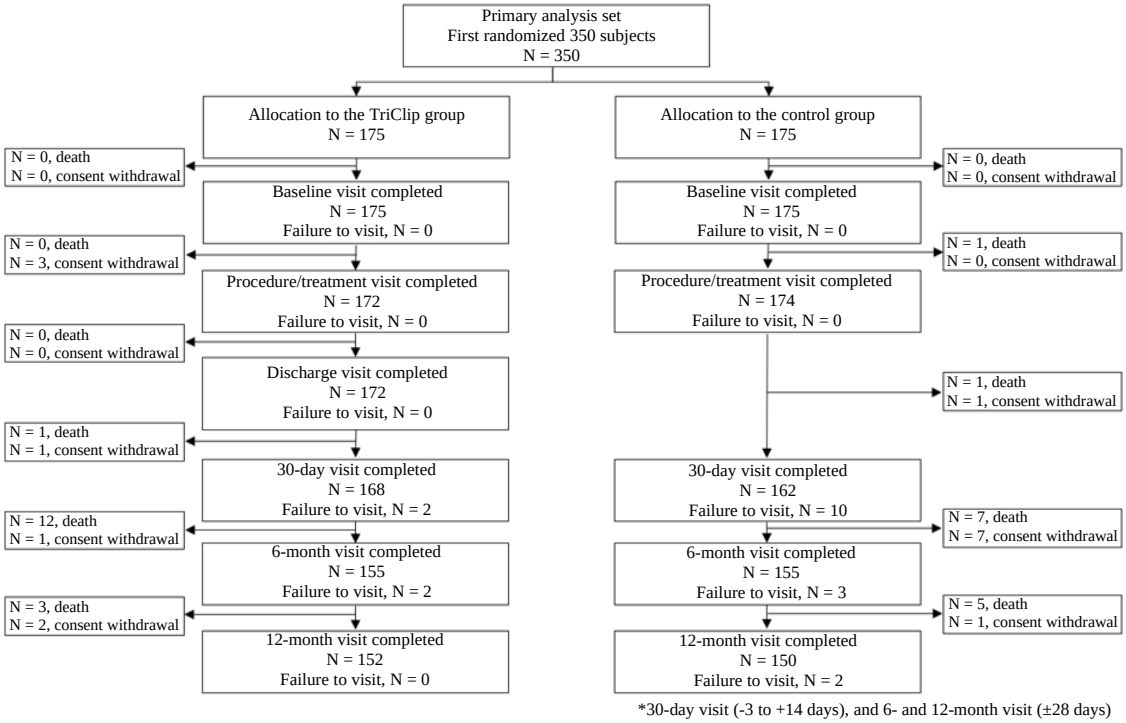


Figure 5. Subject follow-up status (randomized cohort)

The primary endpoint for the randomized cohort was a hierarchical composite of all-cause death or tricuspid valve surgery, cardiac failure hospitalizations, and quality of life (QOL) improvement assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 12 months post-procedure. The superiority of the TriClip therapy over the control therapy was assessed. The primary endpoint of the TriClip group was compared with that of the control group in the following hierarchical order using the Finkelstein-Schoenfeld test that analyzes prioritized composite endpoints by giving the priority to the more clinically important event:

a. Time to all-cause death or tricuspid valve surgery
b. Number of cardiac failure hospitalizations
c. KCCQ score improvement of ≥15 points compared with baseline

The results of the primary endpoint were estimated based on the results of assessment with the assumptions shown below. With a sample size of 350, [redacted] for the primary endpoint. Accordingly, the sample size was determined to be 350 for the evaluation of the primary endpoint.

[redacted]

i. Patient characteristics

Table 8 presents the characteristics of the patients enrolled in the randomized cohort. Table 9 presents their baseline echocardiographic data. There was no particular difference between the groups.

Table 8. Patient characteristics (randomized cohort)

Item	TriClip (N = 175)	Control (N = 175)
Age (years)	78.0 ± 7.4 (175)	77.8 ± 7.2 (175)
Female	56.0% (98/175)	53.7% (94/175)
BMI (kg/m^2)	27.0 ± 5.8 (175)	26.9 ± 5.2 (175)
Medical history		
Dyslipidaemia	66.9% (117/175)	52.6% (92/175)
Hypertension	81.1% (142/175)	80.6% (141/175)
Cerebrovascular accident	6.3% (11/175)	11.4% (20/175)
Transient ischaemic attack	7.4% (13/175)	9.7% (17/175)
Chronic obstructive pulmonary disease	10.9% (19/175)	13.7% (24/175)
Diabetes mellitus	16.0% (28/175)	15.4% (27/175)
Renal illness	35.4% (62/175)	35.4% (62/175)
Hepatic illness	6.3% (11/175)	9.1% (16/175)
Peripheral vascular disease	9.1% (16/175)	10.3% (18/175)
Atrial fibrillation	87.4% (153/175)	93.1% (163/175)
CABG	17.7% (31/175)	20.6% (36/175)
PCI	14.9% (26/175)	13.1% (23/175)
CRT/CRT-D/ICD/permanent pacemaker	16.0% (28/175)	13.7% (24/175)
Cardiac failure hospitalization within 12 months prior to enrollment	25.1% (44/175)	25.1% (44/175)
Prior aortic valve intervention	15.4% (27/175)	15.4% (27/175)
Prior mitral valve intervention	25.7% (45/175)	24.0% (42/175)
Prior pulmonary aortic valve intervention	0.0% (0/175)	0.6% (1/175)
Prior tricuspid valve intervention	0.6% (1/175)	0.6% (1/175)
KCCQ score	56.0 ± 23.4 (175)	54.1 ± 24.2 (174)
6-minute walk distance (m)	240.5 ± 117.1 (164)	253.6 ± 129.1 (169)
NYHA Class		
Class I	0.0% (0/175)	0.0% (0/175)
Class II	40.6% (71/175)	44.6% (78/175)
Class III	57.1% (100/175)	52.0% (91/175)
Class IV	2.3% (4/175)	3.4% (6/175)
Medication use		
β blockers	72.6% (127/175)	73.1% (128/175)
ACE inhibitors or ARBs	42.3% (74/175)	45.1% (79/175)
Vasodilators	10.9% (19/175)	12.0% (21/175)
Diuretics	97.1% (170/175)	98.9% (173/175)

Continuous variables are expressed as mean ± standard deviation (SD) (N). Categorical variables are expressed as percentage (n/N).

Table 9. TR assessment based on baseline echocardiography (randomized cohort)

Item	TriClip (N = 175)	Control (N = 175)
TR severity		
Trace	0.0% (0/173)	0.0% (0/165)
Mild	0.0% (0/173)	0.0% (0/165)
Moderate	2.3% (4/173)	1.2% (2/165)
Severe, Grade 3	25.4% (44/173)	29.7% (49/165)
Severe, Grade 4	21.4% (37/173)	18.2% (30/165)
Severe, Grade 5	50.9% (88/173)	50.9% (84/165)
TR etiology		
Secondary	94.8% (165/174)	92.9% (158/170)
Degenerative	2.3% (4/174)	1.2% (2/170)
Mixed	2.9% (5/174)	5.9% (10/170)
Pacemaker-related	0.0% (0/174)	0.0% (0/170)
Coaptation gap (mm)	5.5 ± 1.8 (137)	5.2 ± 1.7 (142)

Continuous variables are expressed as mean ± SD (N). Categorical variables are expressed as percentage (n/N).

ii. Procedural outcomes

Table 10 presents procedural outcomes in the randomized cohort. Of 175 subjects in the TriClip group, 172 subjects underwent the clip placement procedure, and the remaining 3 subjects who withdrew consent prior to the TriClip therapy were excluded. A total of 170 subjects had the clips implanted. The 2 subjects who received no clip consisted of 1 subject for whom the procedure was discontinued because of a mobile blood clot adhering to the right atrium lead and 1 subject in whom several attempts failed to grasp both valve leaflets appropriately. Most subjects received 2 (61.0%) or 3 (24.4%) clips.

Table 10. Procedural outcomes (only the TriClip group in the randomized cohort)

Item	TriClip (N = 172)
Number of implanted clips	2.2 ± 0.7 (172)
0*	1.2% (2/172)
1	10.5% (18/172)
2	61.0% (105/172)
3	24.4% (42/172)
4	2.9% (5/172)
Device used	
TriClip (TriClip G4 System)	52.9% (91/172)
Former generation (TriClip System)	47.1% (81/172)
Total procedure time[b] (min)	151.0 ± 71.7 (171)
Clip placement time[c] (min)	89.7 ± 66.4 (168)
X-ray fluoroscopy time (min)	31.9 ± 23.5 (171)

Continuous variables are expressed as mean ± SD (N). Categorical variables are expressed as percentage (n/N).

* The 2 subjects with failed clip placement during the index procedure had successful clip implantation during the second attempt.

iii. Results of the primary endpoint

Figure 6 presents the results of the primary endpoint. The win ratio in the TriClip group compared with the control group was 1.44 (95% confidence interval [CI] [1.03, 2.08], superiority P = 0.0311), demonstrating the predefined hypothesis (the superiority of the TriClip therapy over the control therapy).

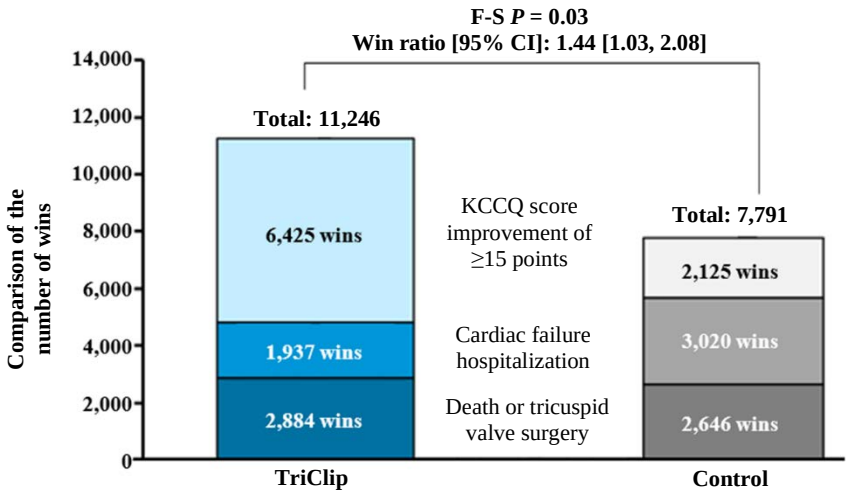


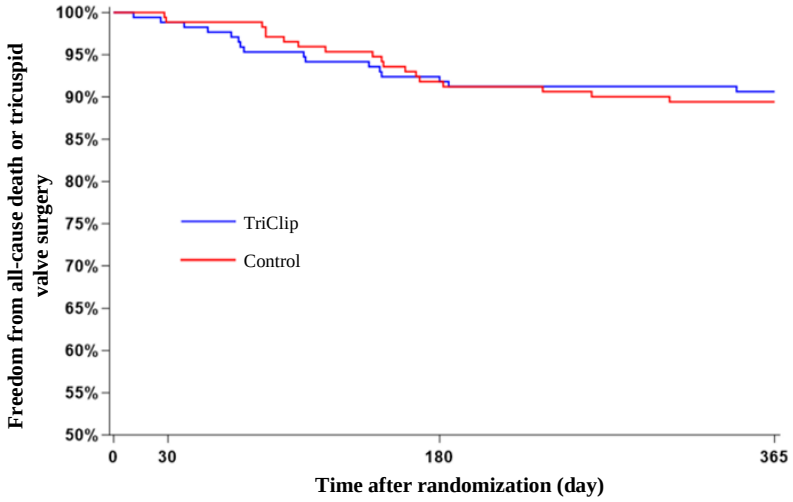
Figure 6. Results of the primary endpoint (randomized cohort)

The results of each component of the primary endpoint are shown below.

[b] Total procedure time: Time from the start of intravascular catheter placement or transesophageal echocardiogram (TEE) to the completion of removal of the last catheter and TEE.

[c] Clip placement time: Time from placement of the SGC in the right atrium to retrieval of the CDS into the SGC.

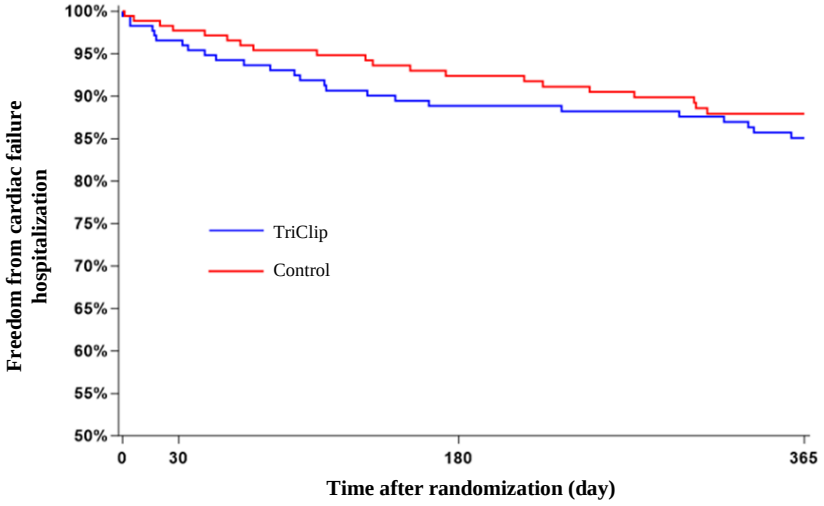
The Kaplan-Meier estimate of the rate of freedom from all-cause death or tricuspid valve surgery through 12 months post-procedure was 90.6% in the TriClip group and 89.4% in the control group (Log-rank test, $P = 0.7556$) (Figure 7).



		Time after randomization (day)				
Allocation	**Data category**	**0**	**30**	**180**	**365**	***P*-value**
TriClip	Number of subjects at risk	175	170	158	152	
	Number of events	0	2	14	16	
	Incidence of events (%)	0.0%	1.2%	8.2%	9.4%	
	Survival rate (%)	100.0%	98.8%	91.8%	90.6%	
	Standard error (%)	0.0%	0.8%	2.1%	2.2%	
	95% CI	[100.0%, 100.0%]	[95.5%, 99.7%]	[86.6%, 95.1%]	[85.2%, 94.2%]	
Control	Number of subjects at risk	175	173	154	149	
	Number of events	0	2	14	18	
	Incidence of events (%)	0.0%	1.1%	8.2%	10.6%	
	Survival rate (%)	100.0%	98.9%	91.8%	89.4%	
	Standard error (%)	0.0%	0.8%	2.1%	2.4%	
	95% CI	[100.0%, 100.0%]	[95.5%, 99.7%]	[86.6%, 95.1%]	[83.8%, 93.2%]	
Log rank						0.7556

Figure 7. Freedom from all-cause death or tricuspid valve surgery through 12 months post-procedure (randomized cohort)

The rate of freedom from cardiac failure through 12 months post-procedure was 84.5% in the TriClip group and 88.0% in the control group (Log-rank test, $P = 0.3244$) (Figure 8).



		Time after randomization (day)				
Allocation	**Data category**	**0**	**30**	**180**	**365**	***P*-value**
TriClip	Number of subjects at risk	175	167	145	134	
	Number of events	0	6	20	26	
	Incidence of events (%)	0.0%	3.4%	11.8%	15.5%	
	Survival rate (%)	100.0%	96.6%	88.2%	84.5%	
	Standard error (%)	0.0%	1.4%	2.5%	2.8%	
	95% CI	[100.0%, 100.0%]	[92.5%, 98.4%]	[82.4%, 92.2%]	[78.0%, 89.2%]	
Control	Number of subjects at risk	175	171	148	138	
	Number of events	0	4	13	20	
	Incidence of events (%)	0.0%	2.3%	7.6%	12.0%	
	Survival rate (%)	100.0%	97.7%	92.4%	88.0%	
	Standard error (%)	0.0%	1.1%	2.0%	2.5%	
	95% CI	[100.0%, 100.0%]	[94.0%, 99.1%]	[87.2%, 95.5%]	[81.9%, 92.1%]	
Log rank						0.3244

Figure 8. Freedom from cardiac failure hospitalization through 12 months post-procedure (randomized cohort)

The percentage of subjects with KCCQ score improvement of ≥15 points at 12 months post-procedure was 49.7% in the TriClip group and 26.4% in the control group (normal approximation of the difference of binomial proportions, $P < 0.0001$) (Figure 9).

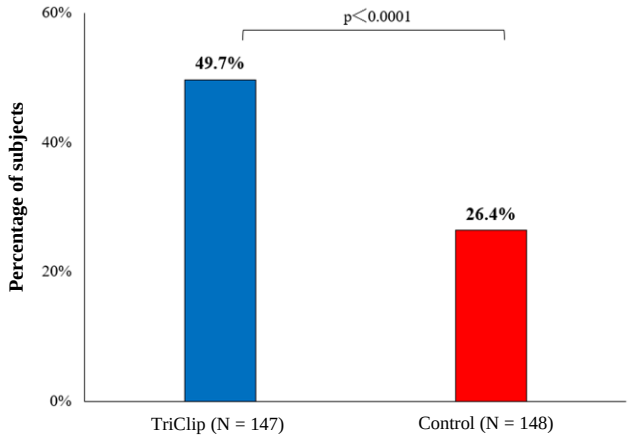


Figure 9. KCCQ score improvement of ≥15 points at 12 months post-procedure (randomized cohort)

iv. Results of secondary endpoints

Table 11 presents the results of the secondary endpoints.

The Kaplan-Meier estimate of the rate of freedom from major adverse events (MAEs) through 30 days post-procedure was 98.3% (the lower limit of 95% CI, 96.3%) in the TriClip group, which met the performance goal (90%) ($P < 0.0001$). This conservative performance goal (90%) was determined based on [redacted].

The change in KCCQ score from baseline at 12 months post-procedure and the percentage of subjects with TR severity reduction to moderate or less at 30 days post-procedure were both significantly greater in the TriClip group than in the control group. The change in 6-minute walk distance showed no particular between-group difference.

Table 11. Results of the secondary endpoints (randomized cohort)

Endpoint (hierarchical order)	TriClip	Control	*P* value	Result
Freedom from MAEs at 30 days post-procedure (Kaplan-Meier estimate)	98.3% (lower limit of 95% CI, 96.3%)	-	<0.0001	Achieved
Change in KCCQ score from baseline at 12 months post-procedure*	12.34 ± 1.75	0.61 ± 1.75	<0.0001	Achieved
Percentage of subjects with TR severity reduction to moderate or less at 30 days post-procedure	87.0% (141/162)	5.4% (8/147)	<0.0001	Achieved
Change in 6-minute walk distance from baseline at 12 months post-procedure*	-8.12 ± 10.50	-25.17 ± 10.31	0.24822	Not achieved

* For subjects who had cardiovascular death related to cardiac failure or underwent tricuspid valve surgery before the completion of the 12-month follow-up, the KCCQ score and 6-minute walk distance at 12 months post-procedure were 0. Least squares means in an ANCOVA model are presented.

Table 12 presents MAEs that occurred through 30 days post-procedure.

Table 12. MAEs through 30 days post-procedure (the TriClip group in the randomized cohort)

MAE component	Incidence of events (N = 172)
Cardiovascular death	0.6% (1/172)
New onset of renal failure	1.2% (2/172)
Endocarditis requiring surgery	0% (0/172)
Non-elective cardiovascular surgery for device-related adverse events post-index procedure	0% (0/172)

v. Adverse events

As presented in Table 13, a total of 28 subjects (15 in the TriClip group, 13 in the control group) in the randomized cohort died by 12 months postoperative. The 15 deaths in the TriClip group included 11 cardiovascular deaths (cardiac failure related events in 7 subjects) and 4 non-cardiovascular deaths (sepsis in 2 subjects, end stage renal disease in 1 subject, and COVID-19 related event in 1 subject). The TriClip group had no device- or procedure-related deaths.

Table 13. CEC-adjudicated adverse events through 12 months post-procedure (randomized cohort)

Event	TriClip (N = 175)					Control (N = 175)		
	No. of events	Incidence	Device-related	Procedure-related	COVID-19-related	No. of events	Incidence	COVID-19-related
All-cause death	15	8.6% (15/175)	0	0	1	13	7.4% (13/175)	0
Cardiovascular (VARC II)	11	6.3% (11/175)	0	0	0	8	4.6% (8/175)	0
Cardiac failure-related	7	4.0% (7/175)	0	0	0	5	2.9% (5/175)	0
Non cardiac failure-related	4	2.3% (4/175)	0	0	0	3	1.7% (3/175)	0
Non cardiovascular (VARC II)	4	2.3% (4/175)	0	0	1	5	2.9% (5/175)	0
Hospitalization	111	36.0% (63/175)	2	7	2	100	34.3% (60/175)	0
Cardiac failure hospitalization	35	14.9% (26/175)	1	2	0	28	11.4% (20/175)	0
Other cardiovascular hospitalization	17	9.1% (16/175)	1	5	0	21	9.1% (16/175)	0
Non cardiovascular hospitalization	59	21.7% (38/175)	0	0	2	51	21.1% (37/175)	0
Adverse events								
Tricuspid valve surgery	3	1.7% (3/175)	2	2	0	6	3.4% (6/175)	0
Percutaneous tricuspid valve intervention*	4	2.3% (4/175)	3	4	0	3	1.7% (3/175)	0
Major breeding (BARC ≥3a)	10	5.7% (10/175)	0	3	0	3	1.7% (3/175)	0
New onset of renal failure	4	2.3% (4/175)	0	1	0	1	0.6% (1/175)	0
Transient ischaemic attack	1	0.6% (1/175)	0	0	0	0	0.0% (0/175)	0
Cerebrovascular accident (VARC II)	3	1.7% (3/175)	0	0	0	4	1.7% (3/175)	0
Myocardial infarction (VARC II)	0	0.0% (0/175)	0	0	0	0	0.0% (0/175)	0
Endocarditis requiring surgery	0	0.0% (0/175)	0	0	0	0	0.0% (0/175)	0
Non-elective cardiovascular surgery for device-related AEs post-index procedure	0	0.0% (0/175)	0	0	0	0	0.0% (0/175)	0
Cardiogenic shock	0	0.0% (0/175)	0	0	0	1	0.6% (1/175)	0

* Percutaneous tricuspid valve intervention includes reintervention in the TriClip group and the first intervention in the control group (crossover with the TriClip according to the protocol in 2 subjects, implantation of another company's clips in the judgment of the local site in 1 subject).

A total of 219 serious adverse events (SAEs) in the TriClip group reported by sites through 12 months post-procedure included 7 device-related events and 15 procedure-related events (6 device- and procedure-related events) (Tables 14 and 15).

Table 14. Device-related SAEs through 12 months post-procedure (randomized cohort)

Event	Device-related
Total	7
TR	2
SLDA	2
Chordae tendinae rupture	1
Cardiac failure	1
Tricuspid valve repair: Additional clip placement because of SLDA	1

Table 15. Procedure-related SAEs through 12 months post-procedure (randomized cohort)

Event	Procedure-related
Total	15
Access site complication	3
Bleeding	3
TR	2
SLDA	2
Cardiac failure	1
Chordae tendinae rupture	1
Right atrium lead thrombosis	1
Inguinal exudation	1
Hypotension accompanied by tachycardia	1

vi. TR severity

Figure 10 presents the percentages of subjects by TR severity at baseline, 30 days post-procedure, and 12 months post-procedure. In the TriClip group, 90% of the subjects had moderate or less TR at 30 days post-procedure, and the percentage was maintained at 12 months post-procedure (89%). In the control group, 6% and 8% of the subjects had TR severity reduction to moderate or less at 30 days post-procedure and 12 months post-procedure, respectively.

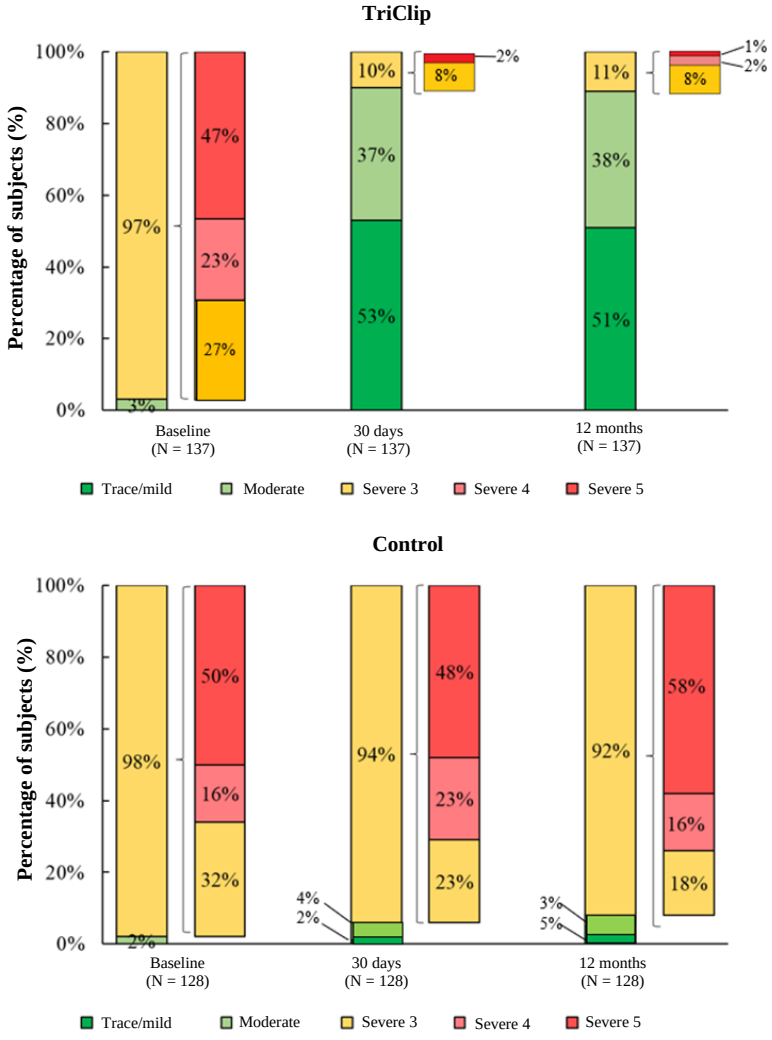


Figure 10. TR severity through 12 months post-procedure (randomized cohort)

vii. Echocardiography

Table 16 presents the change from baseline in 2D echocardiographic measurements at 12 months post-procedure. The effective regurgitant orifice area (EROA) of proximal isovelocity surface area (PISA), PISA regurgitant volume, vena contracta width, and right atrial tricuspid annular plane systolic excursion (TAPSE) tended to show greater reductions in the TriClip group than in the control group. The TriClip group tended to have an increase in left ventricular end-diastolic volume and left ventricular end-systolic volume.

Table 16. Change from baseline in 2D echocardiographic measurements at 12 months post-procedure (randomized cohort)

Item	TriClip (N = 175)	Control (N = 175)	Difference [95% CI]
Tricuspid annulus diameter (cm) (end-diastolic apical 4Ch)	-0.09 ± 0.64 (140)	-0.11 ± 0.74 (135)	0.02 [-0.14, 0.19]
EORA of PISA (cm^2)	-0.44 ± 0.33 (115)	-0.04 ± 0.31 (127)	-0.40 [-0.48, -0.32]
PISA regurgitant volume calculation (mL)	-33.84 ± 20.48 (115)	-1.99 ± 23.56 (127)	-31.85 [-37.43, -26.28]
Vena contracta width (cm) (SL, 4Ch)	-0.52 ± 0.48 (139)	0.03 ± 0.44 (136)	-0.54 [-0.65, -0.43]
Right ventricular end-diastolic diameter, mid (4Ch, cm)	-0.18 ± 0.73 (140)	-0.02 ± 0.85 (134)	-0.17 [-0.36, 0.02]
Right ventricular end-diastolic diameter, base (4Ch, cm)	-0.21 ± 0.71 (142)	-0.12 ± 0.76 (134)	-0.09 [-0.26, 0.08]
Right atrial volume (mL) (Single Plane Simpson's)	7.78 ± 55.92 (140)	-2.13 ± 54.14 (136)	9.91 [-3.13, 22.95]
Right ventricular fractional area change (%)	-0.73 ± 8.16 (133)	-0.52 ± 7.38 (125)	-0.21 [-2.12, 1.69]
Left ventricular end-diastolic volume (mL)	3.91 ± 25.02 (129)	-4.80 ± 23.49 (114)	8.70 [2.57, 14.84]
Left ventricular end-systolic volume (mL)	2.31 ± 15.28 (129)	-2.93 ± 12.52 (114)	5.24 [1.72, 8.75]
Right ventricular TAPSE (cm)	-0.13 ± 0.45 (141)	0.00 ± 0.48 (132)	-0.13 [-0.24, -0.02]
Cardiac output (L/min)	-0.05 ± 1.89 (136)	0.03 ± 1.40 (131)	-0.07 [-0.47, 0.33]
LVOT Doppler stroke volume (mL)	-1.58 ± 17.62 (138)	-1.93 ± 16.48 (133)	0.35 [-3.73, 4.43]
Inferior vena cava diameter (cm)	-0.09 ± 0.56 (135)	-0.01 ± 0.56 (136)	-0.08 [-0.21, 0.05]
Tricuspid valve diastolic mean pressure gradient (CW, mmHg)	1.15 ± 1.28 (136)	0.07 ± 0.58 (126)	1.08 [0.84, 1.32]

The change is expressed as mean ± SD (N).

viii. Relationship between KCCQ score change and TR

Figure 11 presents the relationship between KCCQ score change and TR severity at 12 months post-procedure in the overall randomized cohort. Subjects with lower TR severity at 12 months post-procedure had a greater improvement in KCCQ score, showing a relationship between TR and KCCQ score. Subjects with trace/mild or moderate TR at 12 months post-procedure had KCCQ score improvement of ≥10 points.

Figure 12 presents the relationship between KCCQ score change and TR reduction at 12 months post-procedure in the overall randomized cohort. Subjects with TR severity reduction by 1 grade had KCCQ score improvement of 6 points on average, while those with TR severity reduction by ≥2 grades had a greater KCCQ score improvement (20 points on average, 16 points).

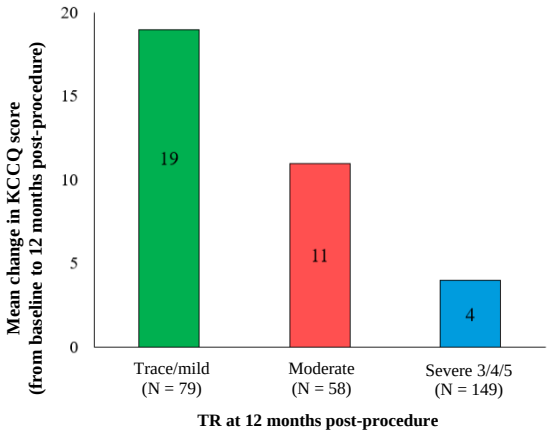


Figure 11. Relationship between TR severity and KCCQ score change (randomized cohort)

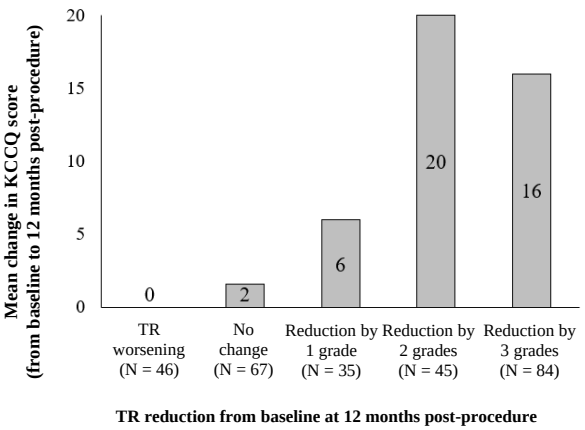


Figure 12. Relationship between TR reduction and KCCQ score change (randomized cohort)

6.A.(1).1).(b) 1- and 2-year results in the full randomized cohort (572 subjects in total) of the US pivotal study (reference data)

The full randomized cohort of the US pivotal study finally enrolled 572 subjects (285 in the TriClip group, 287 in the control group; including the primary analysis set [175 subjects per group]).

i. 1-year results

The win ratio of the primary endpoint in the TriClip group compared with the control group in the full randomized cohort was 1.84 (95% CI [1.40, 2.45], $P < 0.0001$), similar to the result in the primary analysis set (Figure 13).

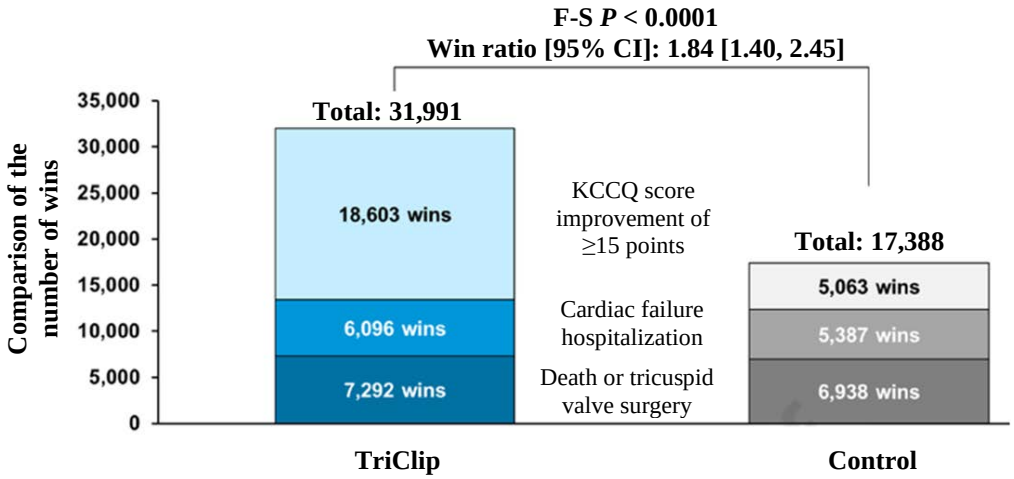


Figure 13. Results of the primary endpoint (full randomized cohort)

Table 17 presents the results of the secondary endpoints. In the TriClip group in the full randomized cohort, the results of all of the secondary endpoints were statistically significant.

Table 17. Results of the secondary endpoints (full randomized cohort)

Item	TriClip (N = 285)	Control (N = 287)	Difference [95% CI]	*P* value
Rate of freedom from MAEs through 30 days post-procedure (Kaplan-Meier estimate)	98.9% (lower limit of 95% CI, 97.7%)	-	-	<0.0001
Change in KCCQ score from baseline through 12 months post-procedure*	13.0 ± 1.4	-0.5 ± 1.4	13.5 [9.5, 17.5]	<0.0001
Percentage of subjects with TR severity reduction to moderate or less at 30 days post-procedure	88.9% (240/270)	5.3% (13/244)	-	<0.0001
Change in 6-minute walk distance from baseline through 12 months post-procedure*	1.7 ± 7.5	-27.4 ± 7.4	31.8 [12.9, 50.6]	<0.0001

* For subjects who had cardiovascular death related to cardiac failure or underwent tricuspid valve surgery before the completion of the 12-month follow-up, the KCCQ score and 6-minute walk distance at 12 months post-procedure were 0. Least squares means in an ANCOVA model are presented.

Figure 14 presents the relationship between TR change and KCCQ score change. Figure 15 presents the relationship between TR change and 6-minute walk distance change. TR reduction correlated with the changes in KCCQ score and 6-minute walk distance.

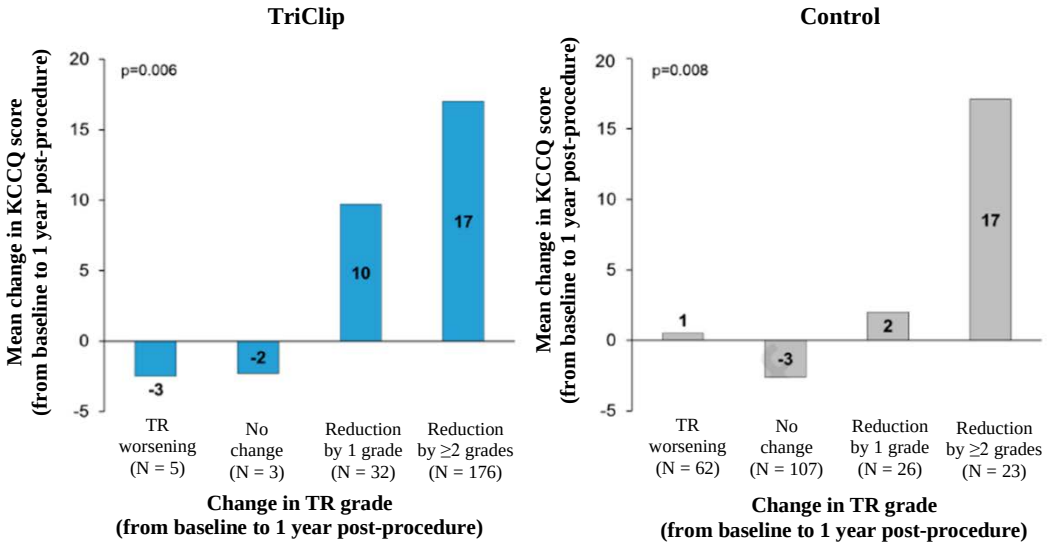


Figure 14. Relationship between TR change and KCCQ score change (full randomized cohort)

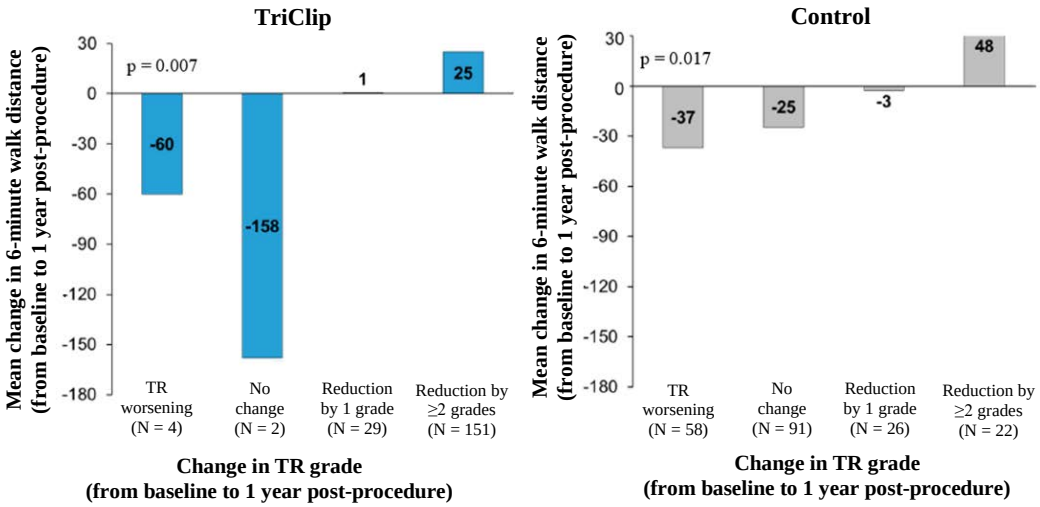


Figure 15. Relationship between TR change and 6-minute walk distance change (full randomized cohort)

ii. 2-year results

Subjects who met the following conditions after the completion of the 1-year follow-up in the control group in the randomized cohort were allowed to cross over to the TriClip therapy:

- Severe TR (as adjudicated by the ECL)
- Meeting anatomical requirements for the TriClip therapy (as adjudicated by the EC)

Of 287 subjects in the control group, 241 subjects completed the 1-year follow-up. A total of 142 subjects (59%) crossed over to the TriClip therapy by the 2-year follow-up.[d] The crossover population had a higher percentage of subjects with Grade 5 TR at 1 year after randomization than that of the non-crossover population that continued medical therapy, with no KCCQ score change and decreased 6-minute walk distance (Table 18).

Table 18. Patient characteristics in the control group (the crossover population and the non-crossover population) at 1 year after randomization

Item	Crossover population (N = 142)	Non-crossover population (N = 99)
TR severity (severe Grade 5)	65.2%	39.1%
Percentage of subjects with NYHA Class III/IV	47.5%	28.9%
Change in KCCQ score (mean ± SD)	-0.19 ± 18.48	8.30 ± 18.17
Change in 6-minute walk distance (mean ± SD)	-21.53 ± 102.77	2.20 ± 89.39
Annualized event rate of cardiac failure hospitalizations (events per subject-year)	0.17	0.12

The rate of freedom from all-cause death or tricuspid valve surgery at 2 years post-procedure was 80.1% in the TriClip group, 79.3% in the control group (ITT), and 79.6% in the control group (censored), showing no significant difference between the TriClip group and the control group (ITT) (Figure 16).

[d] Each subject population in the control group was defined as follows:
- Control group: ITT population
- Crossover population: Subjects in the control group who received the crossover treatment at 1 year after randomization (subjects treated with the TriClip)
- Non-crossover population: Subjects in the control group who received no crossover treatment (subjects continuously treated with medical therapy)
- Control group (censored): Data from the non-crossover population and data from the crossover population prior to the crossover

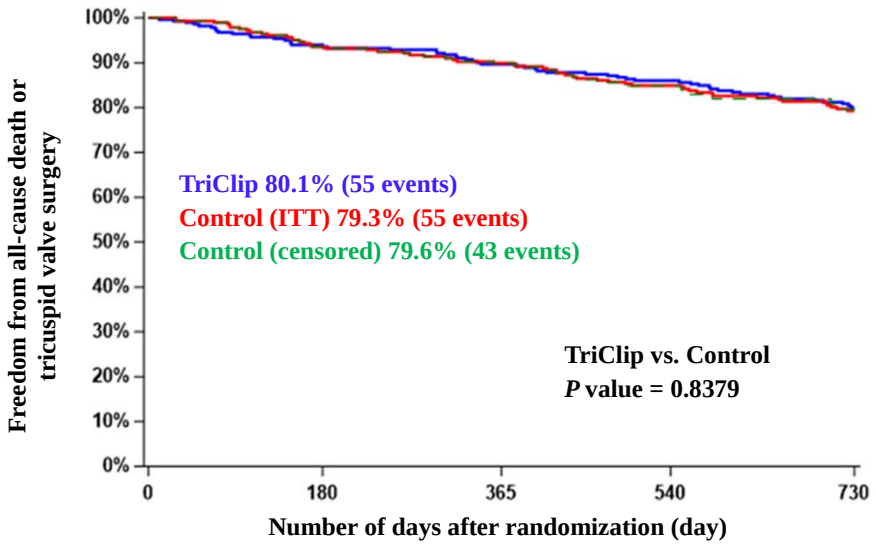


Figure 16. Freedom from all-cause death and tricuspid valve surgery at 2 years post-procedure (full randomized cohort)

The rate of freedom from hospitalization (first cardiac failure hospitalization) and the annualized event rate of cardiac failure hospitalizations (all cardiac failure hospitalizations throughout the follow-up period) were assessed in the analysis of cardiac failure hospitalization.

As presented in Figure 17, the rate of freedom from cardiac failure hospitalization at 2 years post-procedure did not significantly differ between the TriClip group and the control group (ITT). The control group (censored) tended to have a lower rate of freedom from cardiac failure hospitalization.

Figure 18 presents the annualized event rate of cardiac failure hospitalizations at 2 years post-procedure. The TriClip group had a significantly lower annualized event rate of hospitalizations than that in the control group (ITT). The difference in the annualized event rate of cardiac failure hospitalizations was small between the TriClip group and the control group (censored).

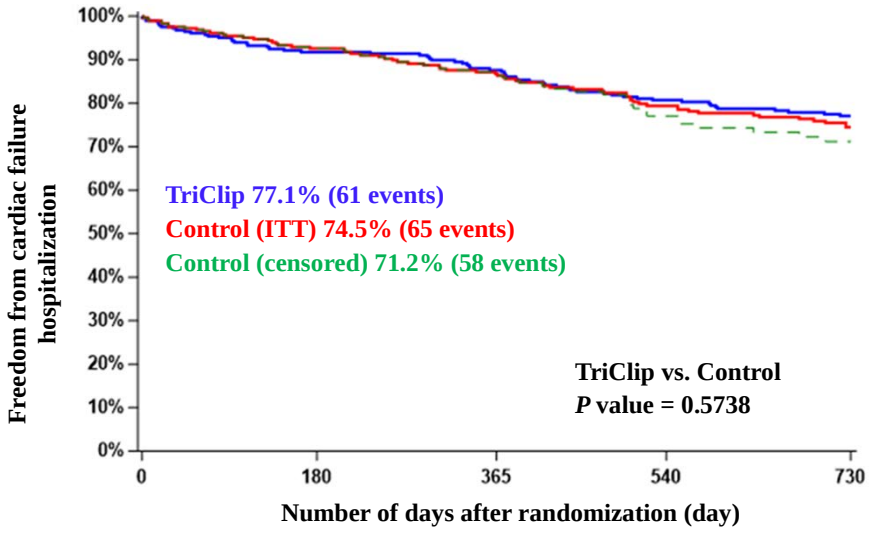


Figure 17. Freedom from cardiac failure hospitalization at 2 years post-procedure (full randomized cohort)

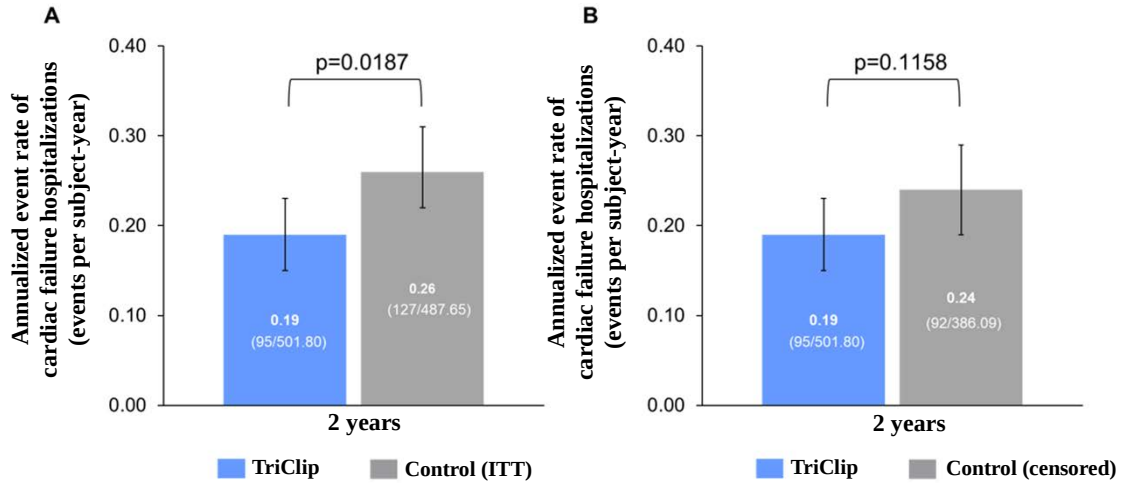


Figure 18. Annualized event rate of cardiac failure hospitalizations through 2 years post-procedure (full randomized cohort)

Figure 19 presents the change in KCCQ score. The TriClip group had a considerable improvement in KCCQ score from the early post-procedure stage, which was maintained through 2 years. A slight improvement (2.2 points) in KCCQ score was shown in the control group (ITT) at 1 year post-procedure but a considerable improvement (12.1 points) in the crossover population. The non-crossover population had a KCCQ score improvement of 10.3 points on average, which was attributable to the fact that this population included subjects in a relatively good condition who did not meet the crossover criteria.

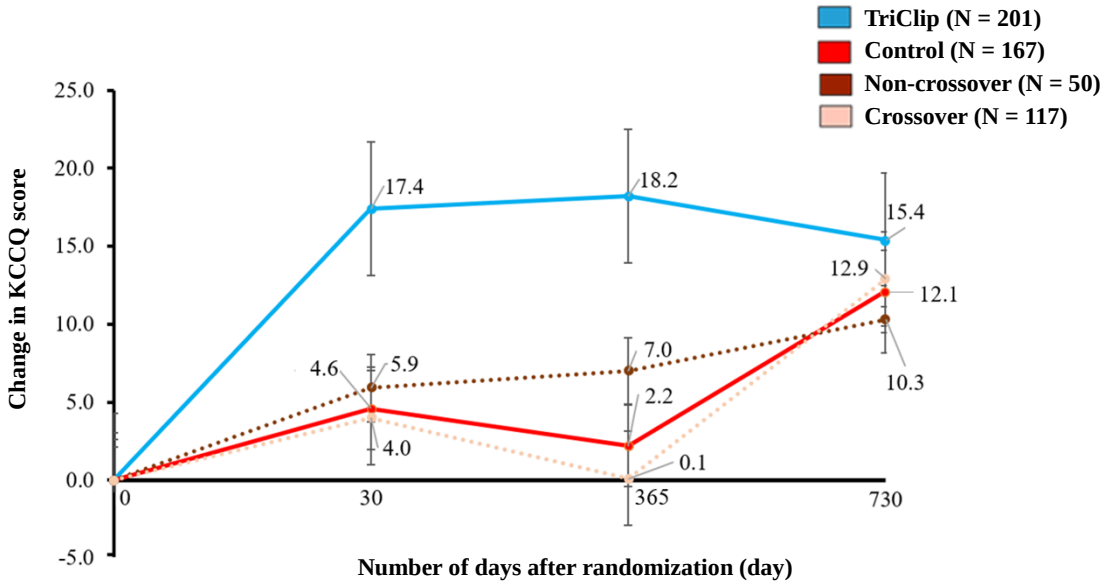
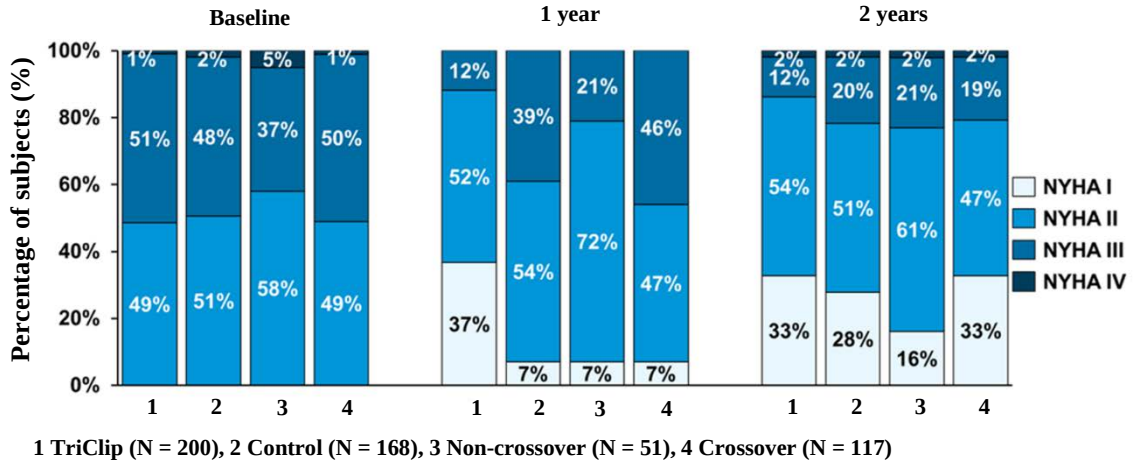


Figure 19. Change in KCCQ score from baseline through 2 years post-procedure (full randomized cohort)

Figure 20 presents New York Heart Association (NYHA) Classes through 2 years post-procedure. In the TriClip group, the percentage of subjects with Class I functional status increased from 0% at baseline to 37% at 1 year post-procedure, and to 33% at 2 years post-procedure. In the control group (ITT), the percentage of subjects with Class I functional status increased from 7% at 1 year post-procedure to 28% at 2 years post-procedure, which was attributable to the fact that the control group included the subjects

with Class I functional status at 2 years post-procedure who accounted for 33% of the crossover population. In the non-crossover population, the percentage of subjects with Class I functional status slightly increased from 0% at baseline to 7% at 1 year post-procedure, and to 16% at 2 years post-procedure.



1 TriClip (N = 200), 2 Control (N = 168), 3 Non-crossover (N = 51), 4 Crossover (N = 117)

Figure 20. NYHA Class through 2 years post-procedure (full randomized cohort)

Table 19 presents the incidence of CEC-adjudicated all-cause deaths, hospitalizations, and tricuspid valve interventions in the full randomized cohort. The incidences of all-cause deaths and hospitalizations at 1 and 2 years post-procedure were comparable in the TriClip group and the control group (ITT). The incidence of percutaneous tricuspid valve interventions was high in the control group (ITT) at 2 years post-procedure because of the crossover.

Table 19. Incidence of CEC-adjudicated all-cause deaths, hospitalizations, and tricuspid valve interventions (full randomized cohort)

Event	1-year incidence		2-year incidence	
	TriClip (N = 285)	Control (N = 287)	TriClip (N = 285)	Control (N = 287)
All-cause death	8.6% (24)	8.0% (22)	17.9% (49)	17.1% (45)
Cardiovascular (VARC II)	5.8% (16)	4.0% (11)	12.4% (33)	9.6% (24)
Cardiac failure-related	4.4% (12)	2.9% (8)	8.8% (23)	7.3% (18)
Non cardiac failure-related	1.5% (4)	1.1% (3)	4.0% (10)	2.4% (6)
Non cardiovascular (VARC II)	3.0% (8)	4.1% (11)	5.8% (15)	8.3% (21)
Hospitalization	35.6% (99)	33.1% (92)	58.8% (161)	54.0% (146)
Cardiac failure hospitalization	12.4% (34)	13.2% (36)	22.9% (61)	25.5% (65)
Other cardiovascular hospitalization	9.6% (26)	6.5% (18)	19.2% (49)	15.3% (38)
Non cardiovascular hospitalization	24.2% (66)	22.0% (60)	39.6% (105)	37.5% (98)
Tricuspid valve surgery	1.8% (5)	2.5% (7)	2.3% (6)	4.3% (11)
Percutaneous tricuspid valve intervention	2.6% (7)	1.6% (4)	3.8% (10)	61.5% (142)

6.A.(1).1).(c) Biomarker tests (reference data)

To assess the effect of the TriClip therapy on renal and hepatic function, the TriClip group (285 subjects) and the control group (287 subjects) in the full randomized cohort received biomarker tests. Changes in laboratory findings at baseline were compared with those at 12 months post-procedure. The TriClip group showed more favorable changes in serum creatinine, estimated glomerular filtration rate (eGFR), serum sodium, and model for end-stage liver disease excluding international normalized ratio (INR) (MELD-XI) score (Table 20).

Table 20. Changes in laboratory findings at 12 months post-procedure (full randomized cohort)

Item	Baseline laboratory finding			Change at 12 months post-procedure		
	TriClip (N = 285)	Control (N = 287)	*P* value	TriClip (N = 285)	Control (N = 287)	*P* value
Serum creatinine (mg/dL)	1.31 ± 0.51	1.26 ± 0.49	0.2279	**-0.01 ± 0.34**	**0.06 ± 0.27**	**0.0141**
eGFR (mL/min/1.73 m^2)	55.6 ± 21.1	57.7 ± 20.8	0.2325	**0.21 ± 13.16**	**-2.55 ± 13.94**	**0.0209**
BUN (mg/dL)	29.7 ± 17.8	29.2 ± 15.6	0.7051	-0.15 ± 14.35	0.74 ± 14.11	0.4796
BUN/creatinine ratio	22.6 ± 9.0	23.3 ± 8.1	0.3310	0.35 ± 10.77	-0.30 ± 8.44	0.4390
Serum sodium (mmol/L)	138.6 ± 3.5	138.9 ± 3.2	0.2830	**0.31 ± 3.54**	**-0.29 ± 3.02**	**0.0387**
INR	1.6 ± 0.7	1.7 ± 1.1	0.9269	0.02 ± 0.85	-0.01 ± 1.03	0.6890
Total bilirubin (mg/dL)	0.88 ± 0.60	0.90 ± 0.59	0.2859	-0.04 ± 0.39	-0.01 ± 0.44	0.5017
ALT (U/L)	21.6 ± 15.9	20.8 ± 10.6	0.7925	-0.82 ± 16.48	-0.97 ± 9.7	0.8983
AST (IU/L)	27.7 ± 11.6	26.3 ± 9.5	0.1022	-0.46 ± 11.1	-0.08 ± 8.1	0.6542
GGT (U/L)	86.9 ± 98.3	79.0 ± 75.3	0.9624	-10.6 ± 68.1	-1.93 ± 50.8	0.1628
MELD-XI score	13.0 ± 3.5	12.7 ± 3.6	0.1688	**-0.16 ± 2.25**	**0.46 ± 2.09**	**0.0012**

The data are expressed as mean ± SD.

6.A.(1).2) Imaging sub-study (reference data)

To assess TR severity reduction and cardiac reverse remodeling in TriClip-treated subjects, an imaging sub-study using MRI or computed tomography (CT) was conducted. The imaging sub-study included 69 subjects who were enrolled in the US pivotal study and consented to participation in the sub-study (31 in the TriClip group, 38 in the control group). The subjects had to undergo CT and MRI scans at baseline and 30 days post-procedure, while they had to undergo CT scans alone at 12 months post-procedure.

6.A.(1).2).(a) Cardiac MRI

Figure 21 presents changes in TR regurgitant volume and regurgitant fraction at 30 days post-procedure. The TriClip group had a TR regurgitant volume reduction of 34 mL and a regurgitant fraction reduction of 25%, while the control group had no change in either parameter.

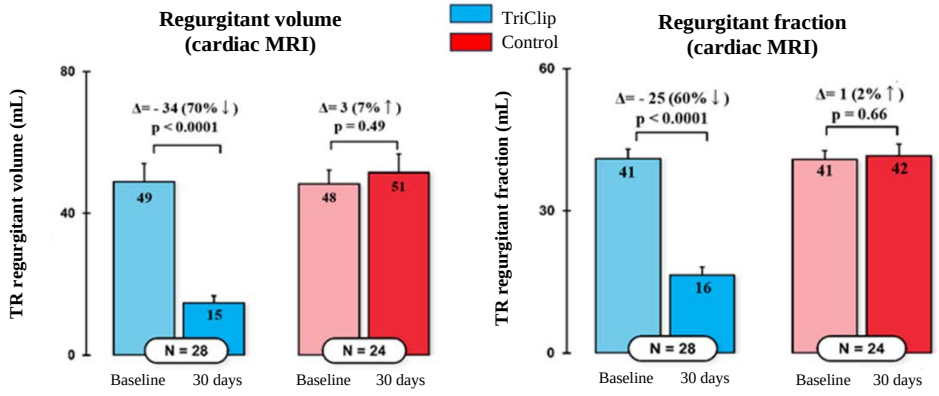


Figure 21. Changes in TR regurgitant volume and regurgitant fraction at 30 days post-procedure

Figure 22 presents a correlation between TR severity reduction and cardiac reverse remodeling based on cardiac MRI findings at 30 days post-procedure. The degree of TR severity reduction correlated with the right atrial and ventricular reverse remodeling and the change in the tricuspid annulus diameter.

There was a strong correlation between the regurgitant volume and the right ventricular end-diastolic volume (RVEDV) (r = 0.90, *P* < 0.0001).

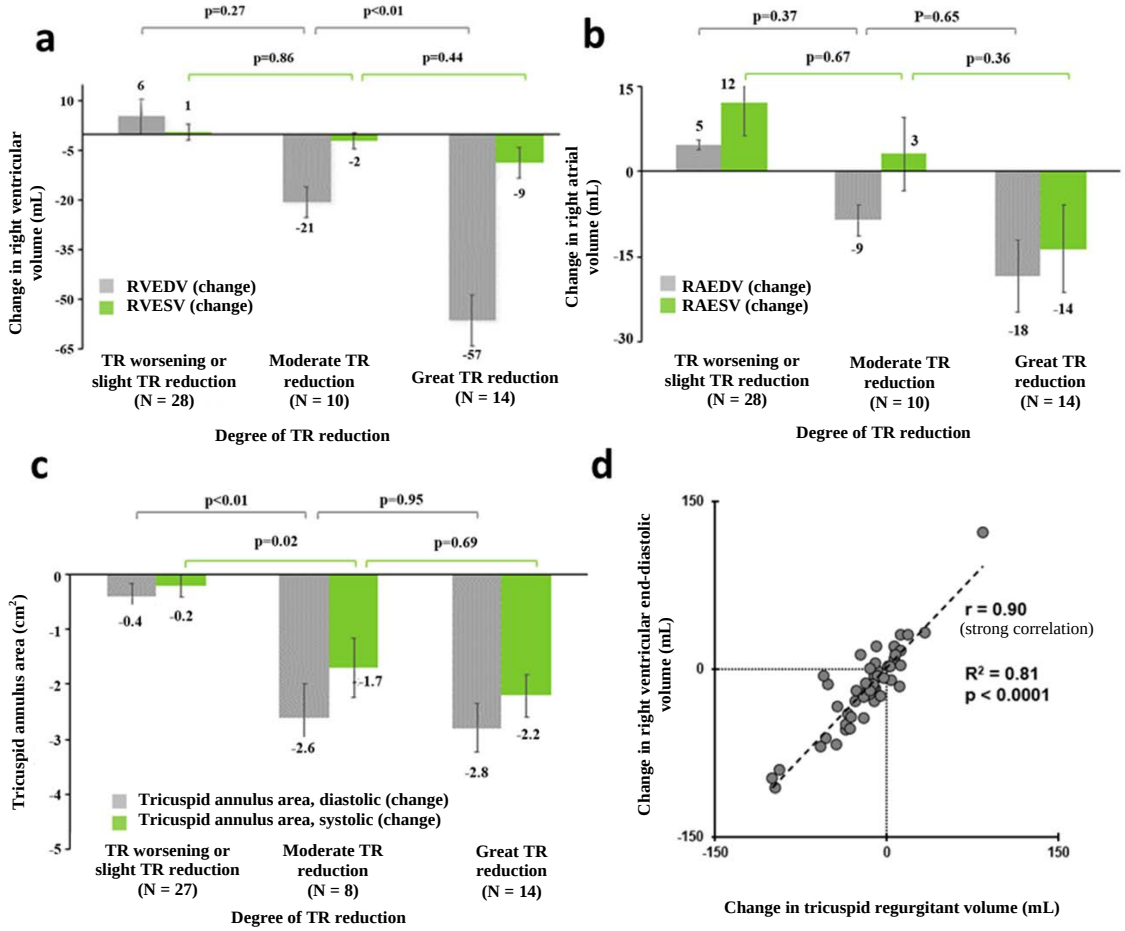


Figure 22. Correlation between TR severity reduction and heart reverse remodeling

(a, Change in right ventricular volume; b, Change in right atrial volume; c, Tricuspid valve ring area; d, Correlation between a change in right ventricular end-diastolic volume and a change in tricuspid valve regurgitant volume)

6.A.(1).2).(b) Cardiac CT

Figure 23 presents a correlation between cardiac reverse remodeling and KCCQ score change based on cardiac CT findings at 30 days and 1 year post-procedure. The TriClip group had a significantly decreased right ventricular volume (12%, *P* < 0.001) and a significantly decreased tricuspid annulus area (11%, *P* < 0.0001) at 30 days post-procedure, which was maintained up to 1 year post-procedure. The control group had no considerable change in the right atrial or ventricular volume, or tricuspid annulus area.

Right atrial reverse remodeling (change from baseline in RVEDV at 1 year post-procedure) correlated with a change in KCCQ score (r = -0.55, *P* = 0.0001).

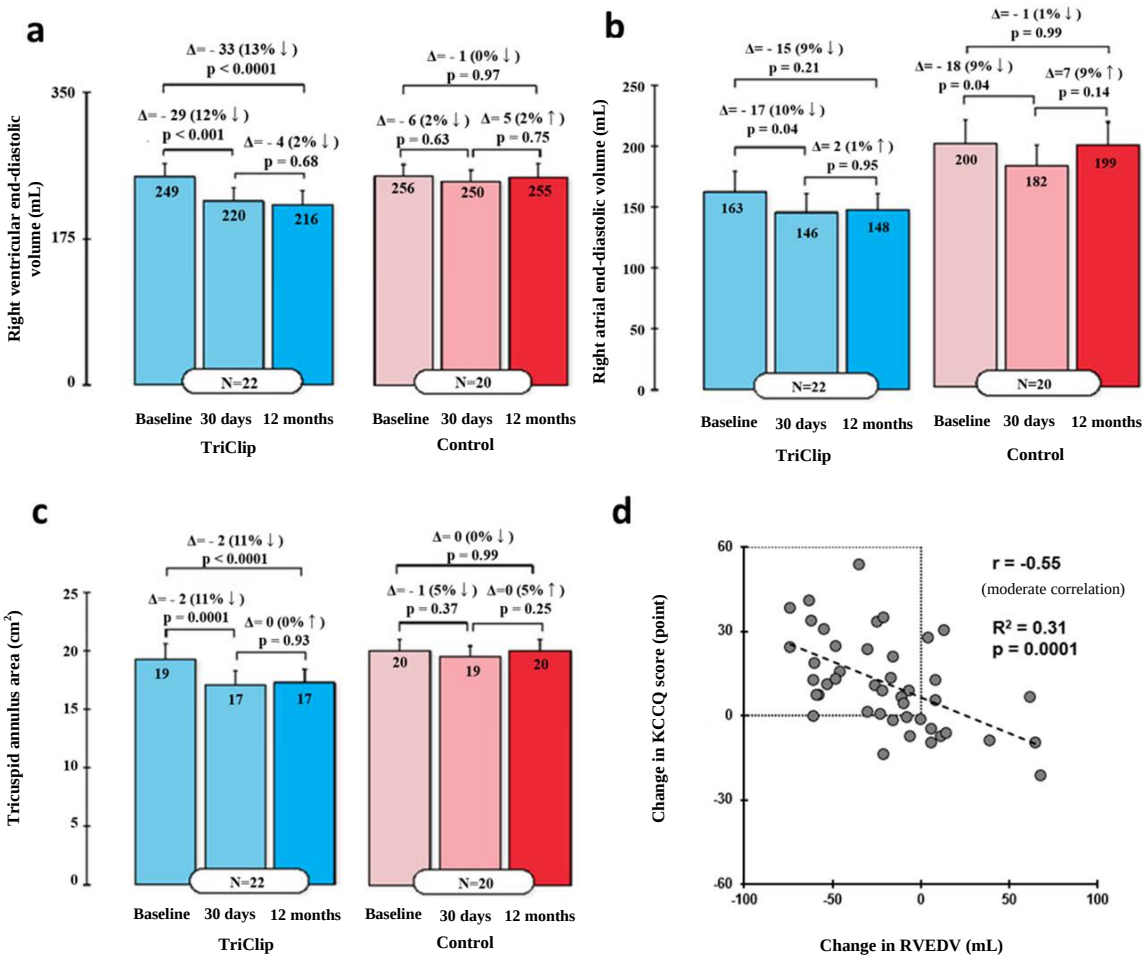


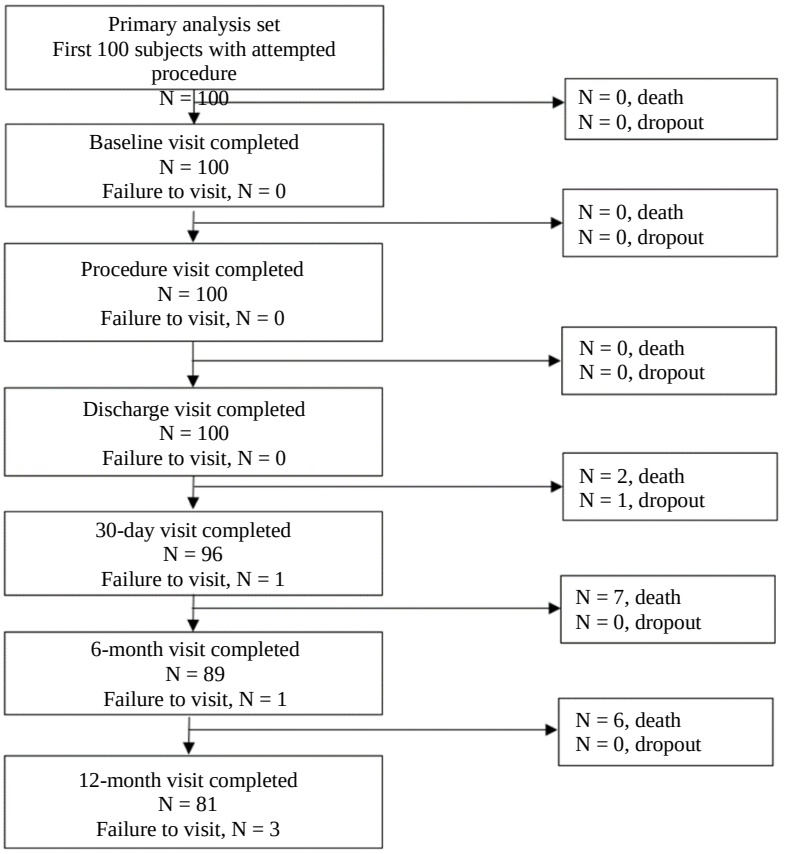
Figure 23. Correlation between cardiac reverse remodeling and KCCQ score change

(a, Right ventricular end-diastolic volume; b, Right atrial end-diastolic volume; c, Tricuspid annulus area; d, Correlation between KCCQ score change and RVEDV change)

6.A.(1).3) Single-arm cohort of the US pivotal study

6.A.(1).3).(a) Single-arm cohort of the US pivotal study (Primary analysis set, 100 subjects), 1-year results

Subjects in whom TriClip was expected to achieve TR severity reduction by at least 1 grade (as determined on a 5-point rating scale) but not to moderate or less (Grade ≤2) as determined by the EC were allocated to the single-arm cohort. Figure 24 presents the follow-up status through 12 months post-procedure.



*30-day visit (-3 to +14 days), and 6- and 12-month visit (±28 days)

Figure 24. Subject follow-up status (single-arm cohort)

The primary endpoint for the single-arm cohort was the rate of survival through 12 months post-procedure with a KCCQ score improvement of ≥10 points from baseline. The results of the primary endpoint in the single-arm cohort were estimated as [redacted], based on the results of assessment with the assumptions shown below. With a sample size of 100, [redacted] for the primary endpoint. Accordingly, the sample size was determined to be 100 for the evaluation of the primary endpoint.

[redacted]

i. Patient characteristics

Table 21 presents the characteristics of the patients enrolled in the single-arm cohort. Table 22 presents their baseline echocardiographic data.

Table 21. Patient characteristics (single-arm cohort)

Item	Single-arm (N = 100)
Age (years)	80.4 ± 6.2 (100)
Female	53.0% (53/100)
BMI (kg/m^2)	26.3 ± 5.3 (100)
Medical history	
Dyslipidaemia	64.0% (64/100)
Hypertension	83.0% (83/100)
Cerebrovascular accident	12.0% (12/100)
Transient ischaemic attack	7.0% (7/100)
Chronic obstructive pulmonary disease	22.0% (22/100)
Diabetes mellitus	18.0% (18/100)
Renal disease	36.0% (36/100)
Hepatic disease	3.0% (3/100)
Peripheral vascular disease	11.0% (11/100)
Atrial fibrillation	93.0% (93/100)
CABG	16.0% (16/100)
PCI	17.0% (17/100)
CRT/CRT-D/ICD/permanent pacemaker	35.0% (35/100)
Cardiac failure hospitalization within 12 months prior to enrollment	22.0% (22/100)
Prior aortic valve intervention	11.0% (11/100)
Prior mitral valve intervention	36.0% (36/100)
Prior pulmonary aortic valve intervention	0.0% (0/100)
Prior tricuspid valve intervention	4.0% (4/100)
KCCQ overall summary score	54.5 ± 22.6 (99)
6-minute walk distance (m)	237.7 ± 120.4 (97)
NYHA Class	
Class I	0.0% (0/100)
Class II	41.0% (41/100)
Class III	53.0% (53/100)
Class IV	6.0% (6/100)
Medication use	
β blocker	74.0% (74/100)
ACE inhibitor or ARB	41.0% (41/100)
Vasodilator	12.0% (12/100)
Diuretic	98.0% (98/100)

Continuous variables are expressed as mean ± SD (N). Categorical variables are expressed as percentage (n/N).

Table 22. TR assessment based on baseline echocardiography (single-arm cohort)

Item	Single-arm (N = 100)
TR severity	
Trace	0.0% (0/96)
Mild	0.0% (0/96)
Moderate	0.0% (0/96)
Severe, Grade 3	9.4% (9/96)
Severe, Grade 4	16.7% (16/96)
Severe, Grade 5	74.0% (71/96)
TR etiology	
Secondary	85.9% (85/99)
Degenerative	5.1% (5/99)
Mixed	4.0% (4/99)
Pacemaker-related	5.1% (5/99)
Coaptation gap (mm)	7.4 ± 2.7 (75)

Continuous variables are expressed as mean ± SD (N). Categorical variables are expressed as percentage (n/N).

ii. Procedural outcomes

Table 23 presents procedural outcomes in the single-arm cohort. A total of 100 subjects allocated to the single-arm cohort underwent the clip placement procedure. Of them, 98 subjects had the clips implanted. The remaining 2 subjects received no clip because of unsuccessful TriClip procedure. One of the subjects had a small grasping area for proper clipping, which made the procedure challenging. However, the subject underwent the second clip placement 5 months later and had the procedure completed (TR

severity reduction from Grade 5 to moderate). The other subject received no clip because of the poor echocardiographic imaging quality of the procedure which was attributable to prior mitral valve replacement. The subject dropped out of the study at 14 days post-procedure. Most subjects received 2 (49.0%) or 3 (35.0%) clips.

Table 23. Procedural outcomes (single-arm cohort)

Item	Single-arm (N = 100)
Number of implanted clips	2.2 ± 0.8 (100)
0	2.0% (2/100)
1	12.0% (12/100)
2	49.0% (49/100)
3	35.0% (35/100)
4	2.0% (2/100)
Device used	
Former generation (TriClip System)	67.0% (67/100)
TriClip (TriClip G4 System)	33.0% (33/100)
Total procedure time (min)	153.5 ± 65.3 (100)
Clip placement time (min)	84.4 ± 58.8 (100)
X-ray fluoroscopy time (min)	33.0 ± 22.3 (99)

Continuous variables are expressed as mean ± SD (N). Categorical variables are expressed as percentage (n/N).

iii. Results of the primary endpoint

Table 24 presents the results of the primary endpoint in the single-arm cohort. The primary endpoint of "rate of survival through 12 months post-procedure with KCCQ score improvement of ≥10 points from baseline" was 46.2% (42 of 91 subjects; the lower limit of 98.75% CI, 34.3%), meeting the performance goal (30%) (P = 0.0008).

A total of 15 subjects died by 12 months post-procedure, and 34 subjects survived through 12 months post-procedure with KCCQ score improvement of ≤9 points. A total of 9 subjects were excluded from the analysis because they dropped out of the study prior to the 12-month visit, experienced COVID-19-related hospitalization or death, or had a missing visit or no KCCQ data at 12 months post-procedure.

Table 24. Primary endpoint (single-arm cohort)

	Estimate	Lower limit of 98.75% CI	Performance goal	*P* value*
Rate of survival through 12 months post-procedure with KCCQ score improvement of ≥10 points from baseline	46.2% (42/91)	34.3%	30%	0.0008

* *P* value calculated using the exact test for a binomial proportion at a one-sided significance level of 1.25%

iv. Results of secondary endpoints

Table 25 presents a summary of the secondary endpoints for which performance goals were predefined in the single-arm cohort.

Table 25. Performance goals of secondary endpoints (single-arm cohort)

Item	Performance goal	Summary
TR reduction by ≥1 grade from baseline at 30 days post-procedure	50%	[redacted]
Freedom from MAEs through 30 days post-procedure	80%	[redacted]
All-cause death or tricuspid valve surgery at 12 months post-procedure	65%	[redacted]

Table 26 presents the results of the secondary endpoints in the single-arm cohort. The percentage of subjects with TR severity reduction by at least 1 grade at 30 days post-procedure was 98.9% (lower limit of 95% CI, 93.8%), exceeding the performance goal (50%). The rate of freedom from MAEs through 30 days post-procedure was 100% (the lower limit of 95% CI, 96.3%), exceeding the performance goal (80%). No significant increase was observed in 6-minute walk distance at 12 months post-procedure.

Table 26. Results of secondary endpoints (single-arm cohort)

Endpoint (hierarchical order)	Summary	*P* value	Result
TR reduction by ≥1 grade from baseline at 30 days post-procedure	98.9% (87/88) Lower limit of 95% CI, 93.8%	<0.0001	Achieved
Freedom from MAEs through 30 days post-procedure	100.0% (99/99) Lower limit of 95% CI, 96.3%	<0.0001	Achieved
Change in 6-minute walk distance from baseline at 12 months post-procedure	13.7 ± 92.7 (71) 95% CI [-8.3, 35.6]	0.1090	Not achieved
All-cause death or tricuspid valve surgery at 12 months post-procedure (Kaplan-Meier estimate)	83.7% Lower limit of 95% CI, 74.7%	<0.0001	-*
Cardiac failure re-hospitalization through 12 months post-procedure (annualized event rate)	Pre-procedure: 0.33 [0.23, 0.46] Post-procedure: 0.36 [0.26, 0.51]	0.3480	-*

* Since the performance goal of 6-minute walk distance was not achieved, whether these endpoints were met was not assessed.

v. Adverse events

Table 27 presents CEC-adjudicated adverse events in the single-arm cohort through 12 months post-procedure.

Table 27. CEC-adjudicated adverse events through 12 months post-procedure (single-arm cohort)

Event	Number of events	Incidence of events	Device-related	Procedure-related	COVID-19-related
All-cause death	15	15.0% (15/100)	0	0	1
Cardiovascular (VARC II)	11	11.0% (11/100)	0	0	0
Cardiac failure-related	10	10.0% (10/100)	0	0	0
Non cardiac failure-related	1	1.0% (1/100)	0	0	0
Non cardiovascular (VARC II)	4	4.0% (4/100)	0	0	1
Hospitalization	85	50.0% (50/100)	5	4	1
Cardiac failure hospitalization	33	24.0% (24/100)	1	0	0
Other cardiovascular hospitalization	17	14.0% (14/100)	4	3	0
Non cardiovascular hospitalization	35	26.0% (26/100)	0	1	1
Adverse events					
Tricuspid valve surgery	2	2.0% (2/100)	1	0	0
Percutaneous tricuspid valve intervention	7	7.0% (7/100)	5	4	0
Major breeding (BARC ≥3a)	5	5.0% (5/100)	0	1	0
New onset of renal failure	0	0.0% (0/100)	0	0	0
Transient ischaemic attack	1	1.0% (1/100)	0	0	0
Cerebrovascular accident (VARC II)	0	0.0% (0/100)	0	0	0
Myocardial infarction (VARC II)	0	0.0% (0/100)	0	0	0
Endocarditis requiring surgery	0	0.0% (0/100)	0	0	0
Non-elective cardiovascular surgery for device-related AEs post-index procedure	0	0.0% (0/100)	0	0	0
Cardiogenic shock	1	1.0% (1/100)	0	1	0

Of 163 SAEs in the single-arm cohort reported by study sites through 12 months post-procedure, 5 were device-related events and 8 were procedure-related events (of them, 2 were device- and procedure-related events) (Tables 28 and 29).

Table 28. Device-related SAEs through 12 months post-procedure (single-arm cohort)

Event	Device-related
Total	5
TR	3
Cardiac failure	1
Haemorrhage	1

Table 29. Procedure-related SAEs through 12 months post-procedure (single-arm cohort)

Event	Procedure-related
Total	8
TR	1
Dysphagia in pharyngeal phase	1
Tongue haematoma	1
SLDA	1
Urinary retention	1
Respiratory distress	1
Haemorrhage	1
Hypotension	1

vi. Echocardiography

Table 30 presents the change from baseline in 2D echocardiographic measurements at 12 months post-procedure.

Table 30. Change from baseline in 2D echocardiographic measurements at 12 months post-procedure (single-arm cohort)

Item	Single-arm (N = 100)
Tricuspid annulus diameter (cm) (end-diastolic apical 4Ch)	-0.08 ± 0.71 (78)
EROA of PISA (cm^2)	-0.55 ± 0.30 (65)
PISA regurgitant volume calculation (mL)	-37.52 ± 17.04 (65)
Vena contracta width (cm) (SL, 4Ch)	-0.60 ± 0.46 (78)
Right ventricular end-diastolic diameter, mid (4Ch, cm)	-0.11 ± 0.75 (77)
Right ventricular end-diastolic diameter, base (4Ch, cm)	-0.24 ± 0.72 (77)
Right atrial volume (mL) (Single Plane Simpson's)	8.30 ± 72.98 (78)
Right ventricular fractional area change (%)	-2.19 ± 10.34 (74)
Left ventricular end-diastolic volume (mL)	3.15 ± 23.06 (73)
Left ventricular end-systolic volume (mL)	1.78 ± 11.55 (73)
Right ventricular TAPSE (cm)	-0.06 ± 0.50 (77)
Cardiac output (L/min)	0.04 ± 1.49 (76)
LVOT Doppler stroke volume (mL)	-0.08 ± 17.73 (77)
Inferior vena cava diameter (cm)	-0.22 ± 0.61 (74)
Tricuspid valve diastolic mean pressure gradient (CW, mmHg)	0.73 ± 0.77 (70)

The change is expressed as mean ± SD (N).

6.A.(1).3).(b) 1- and 2-year results in the full single-arm cohort (188 subjects) of the US pivotal study (reference data)

The full single-arm cohort of the US pivotal study finally enrolled 188 subjects, including 100 subjects for the primary analysis set. All subjects underwent clip implantation.

The rate of freedom from all-cause death or tricuspid valve surgery was 85.5% at 1 year post-procedure and 75.4% at 2 years post-procedure. The rate of freedom from cardiac failure hospitalization was 78.5% at 1 year post-procedure and 70.3% at 2 years post-procedure.

Table 31 presents the incidence of CEC-adjudicated all-cause deaths, hospitalizations, and tricuspid valve interventions in the full single-arm cohort.

Table 31. Incidence of CEC-adjudicated all-cause deaths, hospitalizations, and tricuspid valve interventions (full single-arm cohort)

Item	1-year incidence	2-year incidence
All-cause death	13.4% (25)	21.9% (40)
Cardiovascular (VARC II)	10.4% (19)	16.3% (29)
Cardiac failure-related	8.3% (15)	12.6% (22)
Non cardiac failure-related	2.3% (4)	4.2% (7)
Non cardiovascular (VARC II)	3.4% (6)	6.6% (11)
Hospitalization	49.3% (91)	64.1% (117)
Cardiac failure hospitalization	21.5% (39)	29.7% (52)
Other cardiovascular hospitalization	12.9% (23)	20.8% (35)
Non cardiovascular hospitalization	28.7% (51)	41.7% (72)
Tricuspid valve surgery	2.3% (4)	4.2% (7)
Percutaneous tricuspid valve intervention	4.6% (8)	6.0% (10)

6.A.(2) Japanese clinical study (Japan Registry of Clinical Trials [jRCT] No. jRCT2072210125, study period [redacted]) 1-year results

The Japanese clinical study was conducted to confirm the extrapolability of the results of the US pivotal study to Japanese patients. The study used similar inclusion and exclusion criteria to those of the randomized cohort of the US pivotal study. The study enrolled patients with estimated TR severity reduction to moderate or less as determined by the EC. Figure 25 presents the follow-up status through 12 months post-procedure.

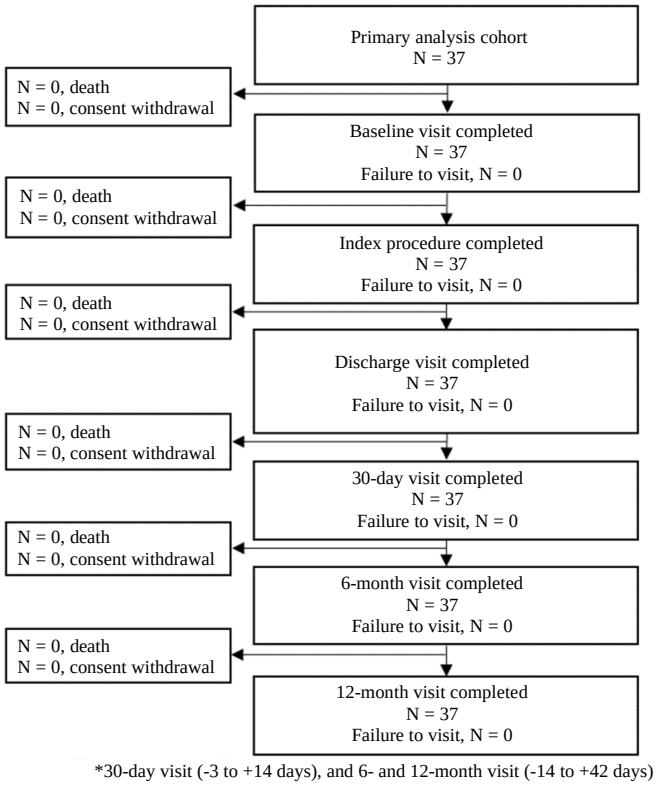


Figure 25. Follow-up status through 12 months post-procedure (Japanese clinical study)

Table 32 presents the primary endpoints and rationale for their performance goals in the Japanese clinical study.

Table 32. Primary endpoints and rationale for their performance goals in the Japanese clinical study

Primary endpoints	Rationale for performance goals
Composite endpoint of freedom from all-cause death or tricuspid valve surgery through 12 months post-procedure	[redacted] was assumed. Accordingly, the performance goal of 62% was determined for the Japanese clinical study.
Annualized event rate of cardiac failure hospitalizations at 12 months post-procedure	The incidence rate of cardiac failure hospitalizations at 1 year post-procedure was estimated to be 0.60 (events per subject-year) because [redacted].

6.A.(2).1) Patient characteristics

Table 33 presents the characteristics of the patients enrolled in the Japanese clinical study. Table 34 presents their baseline echocardiographic data.

Table 33. Patient characteristics (Japanese clinical study)

Item	Japanese clinical study (N = 37)
Age (years)	81.4 ± 5.3 (37)
Female	37.8% (14/37)
BMI (kg/m^2)	21.8 ± 2.8 (37)
Medical history	
Dyslipidaemia	16.2% (6/37)
Hypertension	67.6% (25/37)
Cerebrovascular accident	18.9% (7/37)
Transient ischaemic attack	5.4% (2/37)
Chronic obstructive pulmonary disease	13.5% (5/37)
Diabetes mellitus	16.2% (6/37)
Renal illness	62.2% (23/37)
Hepatic illness	5.4% (2/37)
Atrial fibrillation	100.0% (37/37)
CABG	0.0% (0/37)
PCI	5.4% (2/37)
CRT/CRT-D/ICD/permanent pacemaker	2.7% (1/37)
Cardiac failure hospitalization within prior 12 months	21.6% (8/37)
Prior aortic valve intervention	8.1% (3/37)
Prior mitral valve intervention	27% (10/37)
Prior pulmonary aortic valve intervention	0.0% (0/37)
Prior tricuspid valve intervention	0.0% (0/37)
KCCQ overall summary score	70.2 ± 20.6 (37)
6-minute walk distance (m)	307.4 ± 121.1 (37)
NYHA Class	
Class I	0.0% (0/37)
Class II	73.0% (27/37)
Class III	27.0% (10/37)
Class IV	0.0% (0/37)
Medication use	
β blocker	64.9% (24/37)
ACE inhibitor or ARB	59.5% (22/37)
Vasodilator	0.0% (0/37)
Diuretic	100.0% (37/37)

Continuous variables are expressed as mean ± SD (N). Categorical variables are expressed as percentage (n/N).

Table 34. TR assessment based on baseline echocardiography (Japanese clinical study)

Item	Japanese clinical study (N = 37)
TR severity	
Trace	0.0% (0/37)
Mild	0.0% (0/37)
Moderate	0.0% (0/37)
Severe, Grade 3	8.1% (3/37)
Severe, Grade 4	13.5% (5/37)
Severe, Grade 5	78.4% (29/37)
TR etiology	
Secondary	97.3% (36/37)
Degenerative	0.0% (0/37)
Mixed	2.7% (1/37)
Pacemaker-related	0.0% (0/37)
Coaptation gap (mm)	5.9 ± 1.8 (33)

Continuous variables are expressed as mean ± SD (N). Categorical variables are expressed as percentage (n/N).

6.A.(2).2) Procedural outcomes

Table 35 presents procedural outcomes in the Japanese clinical study. All of the 37 subjects had successful clip placement. Most subjects received 1 (43.2%) or 2 (45.9%) clips.

Table 35. Procedural outcomes (Japanese clinical study)

Item	Japanese clinical study (N = 37)
Number of implanted clips	1.7 ± 0.7 (37)
0	0.0% (0/37)
1	43.2% (16/37)
2	45.9% (17/37)
3	10.8% (4/37)
4	0.0% (0/37)
Total procedure time (min)	183.5 ± 79.5 (37)
Clip placement time (min)	115.3 ± 65.7 (37)
X-ray fluoroscopy time (min)	33.9 ± 24.5 (37)

Continuous variables are expressed as mean ± SD (N). Categorical variables are expressed as percentage (n/N).

6.A.(2).3) Primary endpoints

The Kaplan-Meier estimate of the primary endpoint of "freedom from all-cause death or tricuspid valve surgery through 12 months post-procedure" was 100.0%, meeting the performance goal (62%). The additional primary endpoint was annualized event rate of cardiac failure hospitalizations at 12 months post-procedure. Only 1 cardiac failure hospitalization was reported. Its annualized event rate (events per subject-year) was 0.03 (95% CI, [0.00, 0.15]), meeting the performance goal (0.6).

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

A secondary endpoint was the "percentage of subjects with KCCQ score improvement of ≥15 points at 12 months post-procedure from baseline." This secondary endpoint was achieved when the percentage of subjects with the above improvement were greater than the predefined performance goal (35%). This performance goal was determined based on the result (35%) from the medical therapy group in the COAPT study because no published literature reporting KCCQ score in patients with severe TR who were only on medical therapy was identified at the time of study design. The secondary endpoint was 22.2% (8 of 36 subjects), not meeting the performance goal (35%).

6.A.(2).5) TR severity reduction, KCCQ score, and 6-minute walk distance

The percentage of subjects with TR severity reduction to moderate or less was 80% at 30 days post-procedure and 77% at 12 months post-procedure in the Japanese clinical study. TR severity reduction was maintained.

The change from baseline in KCCQ score at 12 months post-procedure was 9.0 ± 16.2 (N = 37). The change in 6-minute walk distance was -8.4 ± 75.3 (N = 35).

6.A.(2).6) Adverse events

Table 36 presents CEC-adjudicated adverse events through 12 months post-procedure in the Japanese clinical study. No death occurred through 12 months post-procedure.

Table 36. CEC-adjudicated adverse events through 12 months post-procedure (Japanese clinical study)

Event	Number of events	Incidence of events	Device-related	Procedure-related	COVID-19-related
Hospitalization					
Cardiac failure hospitalization	1	2.7% (1/37)	0	0	0
Other cardiovascular hospitalization	2	2.7% (1/37)	0	0	0
Non cardiovascular hospitalization	15	18.9% (7/37)	0	0	1
Adverse events					
Percutaneous tricuspid valve intervention	1	2.7% (1/37)	1	1	0
Major breeding (BARC ≥3a)	4	10.8% (4/37)	0	3	0

A total of 25 SAEs reported through 12 months post-procedure in the Japanese clinical study included no device-related events and 4 procedure-related events (Table 37).

Table 37. Procedure-related SAEs through 12 months post-procedure (Japanese clinical study)

Event	Procedure-related
Total	4
Haemorrhage	1
SLDA	1
Gastrointestinal haemorrhage	1
Streptococcal bacteraemia	1

6.A.(2).7) Echocardiography

Table 38 presents the change from baseline in 2D echocardiographic measurements at 12 months post-procedure.

Table 38. Change from baseline in 2D echocardiographic measurements at 12 months post-procedure (Japanese clinical study)

Item	Japanese clinical study (N = 37)
Tricuspid annulus diameter (cm) (end-diastolic apical 4Ch)	-0.47 ± 0.67 (36)
Right ventricular end-diastolic diameter, mid (4Ch, cm)	-0.08 ± 0.61 (36)
Right ventricular end-diastolic diameter, base (4Ch, cm)	-0.34 ± 0.67 (36)
Right atrial volume (mL) (Single Plane Simpson's)	-22.65 ± 54.09 (36)
Right ventricular fractional area change (%)	-1.42 ± 5.99 (36)
Right ventricular TAPSE (cm)	-0.13 ± 0.48 (37)
Cardiac output (L/min)	0.33 ± 0.99 (35)
Tricuspid valve diastolic mean pressure gradient (CW, mmHg)	0.69 ± 0.70 (36)

The change is expressed as mean ± SD (N).

6.A.(3) Feasibility study (NCT No. NCT03227757, study period [redacted])
3-year results (reference data)

The Feasibility study was a prospective, multi-center, single-arm study conducted in the US and Europe. The study enrolled patients with symptomatic moderate or severe TR who were at high risk for tricuspid valve surgery and were eligible for the TriClip therapy, as determined by site heart teams. The study used the first-generation TriClip System. A total of 85 subjects enrolled in the study underwent the clip placement procedure.

The percentage of subjects with TR severity reduction by at least 1 grade was 84.5% at 30 days post-procedure, 86.1% at 6 months post-procedure, 85.7% at 1 year postoperative, 85.7% at 2 years post-procedure, and 91.1% at 3 years post-procedure. At 3 years post-procedure, 80% of the subjects experienced TR severity reduction to moderate or less. The KCCQ score improved compared with baseline. The score improvement was 9.98 ± 25.60 points at 3 years post-procedure. The percentage of

subjects with NYHA Class II or lower was 25.3% at baseline and 82.0% at 3 years post-procedure, showing improvement.

The Kaplan-Meier estimate of all-cause death was 7.3% at 1 year post-procedure, 17.4% at 2 years post-procedure, and 25.5% at 3 years post-procedure. The annualized event rate of cardiac failure hospitalizations (events per subject-year) was 1.36 in 1 year post-procedure, and 0.86 at 1 year post-procedure and 0.63 at 3 years post-procedure.

A total of 20 subjects experienced 23 CEC-adjudicated MAEs through 3 years post-procedure (Table 39).

Table 39. Summary of CEC-adjudicated MAEs through 3 years post-procedure (Feasibility study)

	Data collection period				
	0-30 days	30-180 days	180-365 days	365-730 days	730-1095 days
MAE	1.2% (1/85)	4.8% (4/84)	1.2% (1/84)	10.7% (9/84)	6.0% (5/83)
Cardiovascular death	0.0% (0/85)	3.6% (3/84)	1.2% (1/84)	8.3% (7/84)	3.6% (3/83)
Myocardial infarction	0.0% (0/85)	1.2% (1/84)	0.0% (0/84)	0.0% (0/84)	0.0% (0/83)
Cerebrovascular accident	0.0% (0/85)	0.0% (0/84)	1.2% (1/84)	1.2% (1/84)	1.2% (1/83)
New onset of renal failure	1.2% (1/85)	0.0% (0/84)	0.0% (0/84)	3.6% (3/84)	1.2% (1/83)
Endocarditis requiring surgery	0.0% (0/85)	0.0% (0/84)	0.0% (0/84)	0.0% (0/84)	0.0% (0/83)
Non-elective cardiovascular surgery for device-related AE	0.0% (0/85)	0.0% (0/84)	0.0% (0/84)	0.0% (0/84)	0.0% (0/83)

6.B Outline of the review conducted by PMDA

PMDA's review focused on the following points:

(1) Justification for using the results from the foreign clinical study as pivotal study for evaluation of the efficacy and safety of the TriClip in Japanese patients
(2) Efficacy and safety of the TriClip
(3) Specific risks of the TriClip
(4) Patients eligible for the TriClip
(5) Post-marketing safety measures

6.B.(1) Justification for using the results from the foreign clinical study as pivotal study for evaluation of the efficacy and safety of the TriClip in Japanese patients

The applicant's explanation about the justification for using the results from the US pivotal study as pivotal study for evaluation of the efficacy and safety of the TriClip in Japanese patients:

There is no substantial difference in the etiology (primary TR and secondary TR) and pathology of TR between Europe/US and Japan. To make a diagnosis of TR and develop a TR treatment plan, physicians need to observe patients' symptoms and physical signs, as well as diagnostic imaging, mainly transthoracic echocardiogram (TTE), which is a standard procedure both in Europe/US and Japan. As shown below, there appears to be no substantial difference in the basic treatment policy for TR between the Japanese and foreign clinical practice guidelines for TR, although treatment options for TR are currently being under discussion overseas. Since no significant enough difference to affect the efficacy and safety of the TriClip has been identified, the results from the US pivotal study can be used as pivotal study to evaluate the efficacy and safety of the TriClip in Japanese patients.

- Medical treatment: Both the Japanese and US guidelines classify diuretics as a Class IIa recommendation for the treatment of symptoms (e.g., oedema) of right cardiac failure resulting from

TR, aiming to reduce intravascular volume. Since secondary TR may be reduced by treating its primary disease, these guidelines recommend that secondary TR associated with left cardiac failure be treated according to the etiology and pathology of left cardiac failure, or medical therapy for pulmonary hypertension precede in TR patients with concurrent pulmonary hypertension. Both countries have similar concepts of medical treatment of TR.

- Surgical treatment: Both the Japanese and US guidelines classify tricuspid valve surgery as a Class I recommendation for the treatment of patients with severe TR who undergo left cardiac surgery. These guidelines classify tricuspid valve surgery as a Class II or lower recommendation for the treatment of "symptomatic isolated severe TR despite optimal medical therapy," which was the target disease of the US pivotal study and the Japanese clinical study. Both countries have similar concepts of surgical treatment of the target patient population of the TriClip.

PMDA's view:

The TriClip is indicated for use in patients with symptomatic severe TR whose severity and symptoms persist despite optimal medical therapy and in whom tricuspid valve surgery is not optimal, as determined by a heart team. In accordance with the clinical practice guidelines, etc., no association between ethnic factors and the etiology or pathology of TR has been identified. In addition, the diagnostic process and treatment policy do not substantially differ between Europe/US and Japan. In view of these facts and taking into consideration the comments from the Expert Discussion, the efficacy and safety of the TriClip in Japanese patients can be evaluated using the results from the US pivotal study as pivotal study. However, the primary therapeutic effects in the TriClip group in the randomized cohort of the US pivotal study resulted from TR severity reduction and KCCQ score improvement; and the degree of KCCQ score improvement differed between the US pivotal study and the Japanese clinical study. These findings were potentially attributable to differences in patient characteristics, etc. The risk-benefit balance of the TriClip needs to be discussed comprehensively taking into consideration the patient characteristics and other data [see Section "6.B.(2) Efficacy and safety of the TriClip"].

6.B.(2) Efficacy and safety of the TriClip

The efficacy and safety of the TriClip were evaluated mainly based on the results of the US pivotal study, which consisted of a randomized cohort and a single-arm cohort. The Japanese clinical study was conducted using similar inclusion and exclusion criteria to those of the randomized cohort in order to confirm the extrapolability of the results of the US pivotal study to Japanese patients. Given the background to these studies, the efficacy and safety of the TriClip were evaluated separately for 1) the randomized cohort of the US pivotal study and the Japanese clinical study and 2) the single-arm cohort of the US pivotal study, as well as 3) by the etiology of TR since TR is classified as primary or secondary TR.

6.B.(2).1) Randomized cohort of the US pivotal study and the Japanese clinical study

(a) Study design

PMDA's view on the designs of the randomized cohort of the US pivotal study and the Japanese clinical study:

To evaluate the efficacy and safety of the TriClip, hard endpoints such as survival rate should be primary endpoints of the US pivotal study, while soft endpoints such as QOL should be secondary endpoints.

For the randomized cohort of the US pivotal study, the study was conducted as a randomized medical therapy-controlled study, the study results were analyzed in a hierarchical order from the hard endpoints to the soft endpoints, and blood biomarkers and cardiac remodeling, which are relevant to the pathology of TR, were also assessed. Taking into account the study design, the efficacy of the TriClip can be comprehensively evaluated.

The Japanese clinical study should have used the same endpoints as those for the randomized cohort of the US pivotal study because the objective of the Japanese clinical study was to assess the extrapolability of the US data to Japanese patients. However, PMDA concluded that the design of the Japanese clinical study was also acceptable because the applicant chose a single-arm design from the viewpoint of the feasibility of the study and the primary endpoint included important events, such as death and cardiac failure hospitalization. Nevertheless, whether the results in the randomized cohort show a consistent trend should be reviewed in detail.

(b) Safety

PMDA's view on the safety of the TriClip in the patient populations of the randomized cohort of the US pivotal study and the Japanese clinical study:

In the randomized cohort of the US pivotal study, a secondary endpoint, "rate of freedom from MAEs through 30 days post-procedure" was 98.3%, meeting the performance goal (Table 11). The TriClip group and the control group had a similar tendency for adverse events, such as death and cardiac failure hospitalization, at 1 and 2 years post-procedure. In addition, the Japanese clinical study revealed no adverse event specific to Japanese subjects. Taking into consideration the comments from the Expert Discussion, PMDA concluded that the safety of the TriClip was clinically acceptable in this patient population. Nevertheless, post-marketing safety measures, such as provision of training programs, should be taken to minimize procedural risks of the TriClip since procedure-related breeding, re-interventions due to single leaflet device attachment (SLDA), etc. were reported [see Section "6.B.(3) Specific risks of the TriClip"].

(c) Efficacy

The randomized cohort of the US pivotal study achieved the primary endpoint. However, only the KCCQ score improved in the TriClip group, compared with the control group. The Japanese clinical study also achieved the primary endpoint. The degree of KCCQ score improvement, chosen as a secondary endpoint, in this study was not consistent with that in the US pivotal study. PMDA asked the applicant to explain the following issues:

i. The reason for the lack of difference in the hard endpoints, including all-cause death or tricuspid valve surgery, between the TriClip and control groups in the randomized cohort of the US pivotal study, and the interpretation of the 1-year efficacy results
ii. Interpretation of the 2-year efficacy results in the randomized cohort of the US pivotal study
iii. Interpretation of the efficacy results in the Japanese clinical study based on the results of the US pivotal study

The applicant's explanation:

i. The reason for the lack of difference in the hard endpoints, including all-cause death or tricuspid valve surgery, between the TriClip and control groups in the randomized cohort of the US pivotal study, and the interpretation of the 1-year efficacy results of the TriClip

- All-cause death or tricuspid valve surgery

  Since only limited information was available on the mortality of patients with TR not accompanied by other valve disease, the patient population eligible for the study, at the time of designing the study, the estimated incidence of all-cause death or tricuspid valve surgery at 12 months post-procedure in the control group was mainly [redacted]. However, [redacted] was suggested.

  The number of tricuspid valve surgeries was [redacted].

  Given the above, the smaller incidence of all-cause death or tricuspid valve surgery than that estimated at the time of designing the study appears to have contributed to the lack of difference between the TriClip group and the control group at 1 year post-procedure. However, longer-term clinical data should be evaluated.

- Cardiac failure hospitalization

  Only limited information was available on cardiac failure hospitalization of patients with TR not accompanied by other valve disease, who were the patient population eligible for the study, at the time of designing the study. Thus, the annualized event rate of cardiac failure hospitalizations (events per subject-year) in the control group of the study was estimated to be [redacted]. The annualized event rate of cardiac failure hospitalizations within 12 months pre-procedure in the study was 0.32, which [redacted]. The annualized event rate at 12 months post-procedure was 0.22 in the TriClip group and 0.17 in the control group. The TriClip group tended to have a higher rate of cardiac failure hospitalizations. This trend was reversed in the full randomized cohort (0.17 in the TriClip group, 0.19 in the control group) without a between-group difference.

  Unlike the data used in the estimation, [redacted] appears to have contributed to these results. As with the results of all-cause death or tricuspid valve surgery discussed earlier, however, longer-term clinical data should be evaluated.

- KCCQ score improvement

  The TriClip group had a similar degree of KCCQ score improvement (12.0 ± 25.8 points with imputation, 15.2 ± 22.3 points without imputation) to that reported in COAPT study (12.5 ± 1.8 points, with a similar imputation). The improvement was greater than the threshold (10 points), which is recommended by the Mitral Valve Academic Research Consortium as a cut-off value of a clinically significant improvement,[19] indicating the sufficient therapeutic efficacy of the TriClip.

  In addition, the TriClip group had more subjects with KCCQ score improvement of ≥15 points and less subjects with decreased KCCQ scores through 12 months post-procedure than those in the control group (18.4% in the TriClip group, 39.9% in the control group).

  Many patients with severe TR are untreated for the following reasons: Tricuspid valve surgery is a high risk surgery; some patients do not respond to medical therapy; and only limited treatment options are available for patients with severe TR. The 1-year results of the US pivotal study showed an excellent safety profile of the TriClip, improvements in QOL and symptoms associated with TR reduction, and an improving tendency of cardiac reverse remodeling and renal/hepatic functions. The study demonstrated the superiority of the TriClip therapy over medical therapy.

ii. Interpretation of the 2-year efficacy results in the randomized cohort of the US pivotal study

In this study, subjects with symptomatic severe TR at 1 year after randomization in the control group were allowed to cross over to the TriClip therapy. The crossover population, which included subjects whose condition worsened compared with the non-crossover population, received intervention with the TriClip later than the non-crossover population. Nevertheless, the crossover population had a similar mortality rate at 2 years post-procedure to that in the non-crossover population, showing the efficacy including improvements in TR severity, QOL, and cardiac failure symptoms.

The 2-year results in the TriClip group in the full randomized cohort showed persistent TR severity reduction, and sustainable improvements in QOL and cardiac failure symptoms beyond 1 year post-procedure. The results in the TriClip group and the control group (ITT) showed no difference in the freedom from all-cause death or tricuspid valve surgery, or in the freedom from cardiac failure hospitalization. However, the TriClip group showed a decreased annualized event rate of cardiac failure hospitalizations. The reduced number of hospitalizations per patient is a patient's benefit.

iii. Interpretation of the efficacy results in the Japanese clinical study based on the results of the US pivotal study

The primary endpoint, "freedom from all-cause death or tricuspid valve surgery through 12 months post-procedure," and the additional primary endpoint, "annualized event rate of cardiac failure hospitalizations at 12 months post-procedure," in the Japanese clinical study met their predefined performance goals.

The secondary endpoint, "percentage of subjects with KCCQ score improvement of ≥15 points at 12 months post-procedure" did not meet the performance goal, which was mainly attributable to a higher baseline KCCQ score than estimated (baseline KCCQ score in the TriClip group, 56.0 ± 23.4 in the

randomized cohort of the US pivotal study and 70.2 ± 20.6 in the Japanese clinical study). Taking into consideration that the score is scaled on a scale of 0 to100, there appears to have been a limited degree of improvement. A similar phenomenon was observed in the US pivotal study. Subjects with high baseline KCCQ scores had poor improvement (Figure 26).

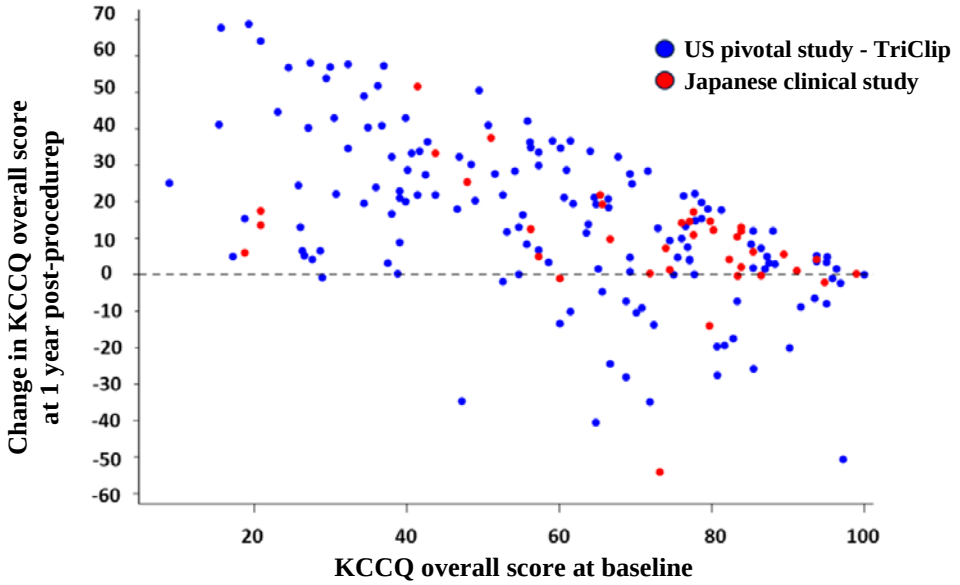


Figure 26. Comparison of the change in KCCQ score at 12 months post-procedure between the studies

In the Japanese clinical study, 50% of the subjects showed KCCQ score improvement of ≥10 points despite having high baseline KCCQ scores (Figure 27). Not many subjects had decreased KCCQ scores of ≥5 points (6% in the Japanese clinical study, 15% in the US pivotal study).

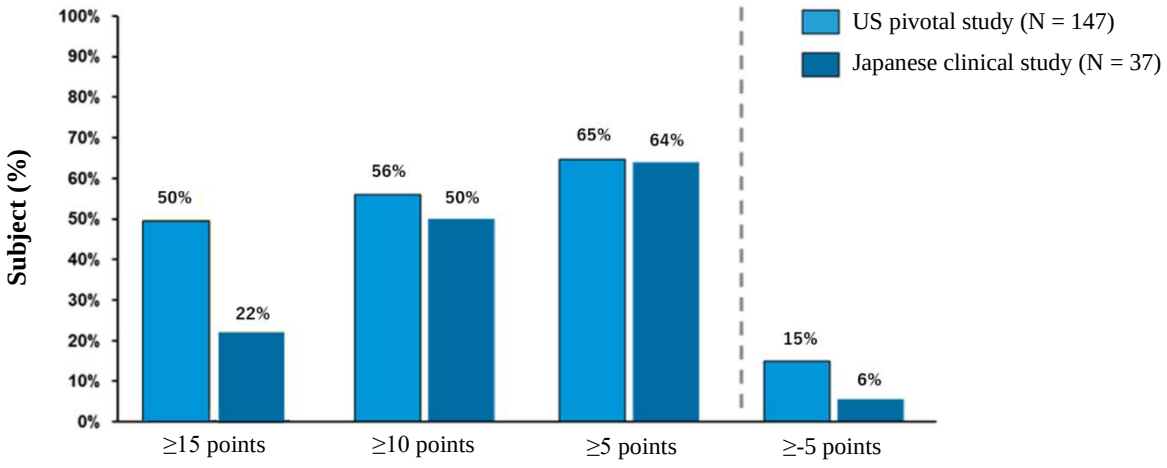


Figure 27. Comparison of KCCQ score at 12 months post-procedure between the US pivotal study and the Japanese clinical study

The secondary endpoint regarding the percentage of subjects with KCCQ score improvement in the Japanese clinical study did not meet the performance goal. However, the TriClip therapy is also expected to reduce TR severity in Japanese patients to improve QOL and cardiac failure symptoms for the following reasons: (i) The percentage of subjects with KCCQ score improvement of ≥10 points in the

Japanese clinical study was consistent with that in the US pivotal study; (ii) the results in the full randomized cohort of the US pivotal study showed a correlation between TR severity reduction and improvement in KCCQ score and 6-minute walk distance (Figures 14 and 15); and (iii) the Japanese clinical study also showed a higher percentage of subjects with a reduction of severe TR to moderate or less.

PMDA's view:
The efficacy of the TriClip in the randomized cohort of the US pivotal study was shown mainly based on QOL (KCCQ score) improvement. This outcome needs to be carefully interpreted because (1) the effect of bias introduced by each subject cannot be ruled out in an open-label study, and (2) the TriClip therapy involves an invasive procedure under general anesthesia, which may cause complications requiring additional intervention.

The results of the US pivotal study do not show that the TriClip reduced TR severity to improve the prognosis of subjects. Currently, however, no effective therapy is available for the target patient population of the TriClip. Taking into consideration the study findings shown below and the comments from the Expert Discussion, the risk-benefit balance of the TriClip could be maintained in appropriately selected eligible patients.

- The study has demonstrated that the TriClip reduced severe TR , contributing to improvement in QOL and symptoms. The study has demonstrated that the TriClip therapy provided persistent TR severity reduction and a sustainable improvement in QOL.
- The study results have suggested that the TriClip was associated with no worsening of prognosis and a decreased annualized event rate of cardiac failure hospitalizations.
- The safety results of the TriClip were favorable.

The degree of KCCQ score improvement in the Japanese clinical study was smaller than that observed in the US pivotal study, but were generally consistent with the results of the US pivotal study. Taking into consideration the comments from the Expert Discussion, PMDA concluded that there was no problem in concluding the efficacy of the TriClip in Japanese patients.

6.B.(2).2) Single-arm cohort of the US pivotal study

(a) Study design

PMDA's view on the design of the single-arm cohort of the US pivotal study:
The single-arm cohort of the US pivotal study enrolled patients with complex tricuspid anatomies who were unlikely to achieve TR severity reduction to moderate or less. This cohort was not expected to benefit from the TriClip therapy as much as the randomized cohort in terms of reduction in death or cardiac failure hospitalization, but was expected to experience improvement in QOL and symptoms. Given this, it is understandable that the primary endpoint was "rate of survival through 12 months post-procedure with KCCQ score improvement of ≥10 points from baseline."

Its performance goal was determined with reference to the results in the medical therapy group in the COAPT study that was conducted in patients with severe MR, because historical data from patients with severe TR, who will be candidates for the TriClip therapy, are limited. However, the pathology and

treatment policy differ between patients with TR and those with MR. As the impact of those differences on clinical outcomes is not clear, it is difficult to assess the appropriateness of the performance goal. PMDA, therefore, concluded that the efficacy and safety of the TriClip in the single-arm cohort should be comprehensively evaluated, together with the results in the randomized cohort.

(b) Efficacy and safety

The applicant's explanation:

The single-arm cohort of the US pivotal study enrolled patients with complex tricuspid anatomies who were unlikely to achieve TR severity reduction to moderate or less. The percentage of subjects with TR severity reduction to moderate or less was 80%, while that of subjects with TR severity reduction to mild or less was 39%. The primary endpoint, "rate of survival through 12 months post-procedure with KCCQ score improvement of ≥10 points from baseline," achieved the performance goal. No MAE, surgical death, embolism, or device thrombosis occurred through 30 days post-procedure.

The results of the single-arm cohort and the randomized cohort of the US pivotal study, and the Japanese clinical study were compared (Table 40).

Table 40. Comparison of the results of studies

Item	US pivotal study Single-arm cohort (N = 100)	US pivotal study TriClip, randomized cohort (N = 175)*	Japanese clinical study (N = 37)
Patient characteristics			
Age	80.4 ± 6.2	78.0 ± 7.4	81.4 ± 5.3
NYHA Class III or IV	59%	59%	27%
KCCQ score	54.5 ± 22.6	56.0 ± 23.4	70.2 ± 20.6
6-minute walk distance (m)	237.7 ± 120.4	240.5 ± 117.1	307.4 ± 121.1
Renal disease	36%	35%	62%
Atrial fibrillation	93%	87%	100%
Cardiac failure hospitalization in prior 1 year	22%	25%	22%
CRT/CRT-D/ICD/permanent pacemaker	35%	16%	3%
Aortic/mitral valve intervention	44%	39%	32%
TR severity			
Severe, Grade 3	9%	25%	8%
Severe, Grade 4	17%	21%	14%
Severe, Grade 5	74%	51%	78%
Etiology - Secondary TR	86%	95%	97%
Coaptation gap (mm)	7.4 ± 2.7	5.5 ± 1.8	5.9 ± 1.8
Right ventricular end-diastolic diameter (base, cm)	5.4 ± 0.9	5.0 ± 0.8	4.7 ± 0.6
Tricuspid annulus diameter (cm)	4.6 ± 0.8	4.3 ± 0.7	4.4 ± 0.6
Right ventricular TAPSE (cm)	1.6 ± 0.4	1.7 ± 0.4	1.8 ± 0.5
Efficacy			
TR severity reduction to moderate or less at 30 days post-procedure	80%	87%	80%
TR severity reduction to moderate or less at 12 months post-procedure	79%	88%	77%
Change in KCCQ score from baseline at 12 months post-procedure	14.5 ± 20.0	15.2 ± 22.3	9.0 ± 16.2
NYHA Class I or II at 12 months post-procedure	80%	84%	95%
Change in 6-minute walk distance from baseline at 12 months post-procedure	13.7 ± 92.7	11.5 ± 111.4	-8.4 ± 75.3
Safety			
At 12 months post-procedure			
All-cause death	15.0%	8.6%	0.0%
Procedure- or device-related	0.0%	0.0%	0.0%
Cardiovascular death	11.0%	6.3%	0.0%
Cardiac failure hospitalization	24.0%	14.9%	2.7%
SLDA	7.0%	7.0%	5.4%

Continuous variables are expressed as mean ± SD. Categorical variables are expressed as percentage.
* For 30 days post-procedure, the results in subjects who underwent the index procedure in the TriClip group (N = 172). For 12 months post-procedure, the results in subjects randomized to the TriClip group (N = 175).

Subjects in the single-arm cohort in the US pivotal study had large right ventricles and tricuspid annulus than those in the randomized cohort and the Japanese clinical study, which suggests a more advanced pathological condition and cardiac remodeling. The US pivotal study demonstrated that the all-cause mortality (15.0%) and the rate of cardiac failure hospitalizations (24.0%) through 12 months post-procedure in the single-arm cohort were approximately double those in the randomized cohort, which is mainly attributable to differences in patient characteristics. The single-arm cohort had KCCQ score improvement comparable to that in the TriClip group in the randomized cohort, indicating that the efficacy and safety of the TriClip are similar in the single-arm cohort and the randomized cohort. As aforementioned, a similar tendency was observed in efficacy and safety results in the randomized cohort and the Japanese clinical study. These findings suggest that the risk-benefit balance of the TriClip can also be ensured in Japanese patients who have similar conditions to the subjects in the single-arm cohort.

PMDA's view:
PMDA understands the applicant's explanation that the differences in patient characteristics between the study populations contributed to the inferior safety profile in the single-arm cohort of the US pivotal study. The results in the single-arm cohort of the US pivotal study showed no particular concerns about the procedural safety, but comparable improvement in QOL and symptoms to that in the randomized cohort, suggesting the clinical significance of the TriClip. The Japanese clinical study did not enroll patients who met the eligibility criteria for the single-arm cohort. Taking into consideration the comments from the Expert Discussion, the indication of the TriClip in Japan could also include patients similar to the patient population of the single-arm cohort provided that adequate post-marketing safety measures including provision of training programs are taken because the Japanese clinical study showed a high procedural success rate.

The long-term outcome of the submitted clinical studies (US pivotal study and Japanese clinical study) should continue to be evaluated in the post-marketing setting and additional risk reduction measures should be taken as necessary, which should be imposed as an approval condition (Approval condition 3).

6.B.(2).3) Assessment by TR etiology

The applicant's explanation about the efficacy and safety of the TriClip by TR etiology:
A subgroup analysis by TR etiology was performed on the results of the randomized cohort and the single-arm cohort of the US pivotal study. Table 41 presents the analysis results of the primary endpoint in the TriClip group in the randomized cohort of the US pivotal study. Table 42 presents the results of efficacy and safety evaluation in the same cohort.

Table 41. Analysis of the primary endpoint in the TriClip group by TR etiology (randomized cohort)

Item	Primary TR (N = 9)	Secondary TR (N = 162)
Incidence of death or tricuspid valve surgery through 12 months post-procedure*	0.0% (0)	9.9% (16)
Incidence of cardiac failure hospitalizations through 12 months post-procedure*	0.0% (0)	16.5% (26)
Percentage of subjects with KCCQ score improvement of ≥15 points at 12 months post-procedure	77.8% (7/9)	47.4% (65/137)

* Calculated from Kaplan-Meier estimates

Table 42. Efficacy and safety results in the TriClip group by TR etiology (randomized cohort)

Item	Time point	Incidence (%)	
		Primary TR (N = 9)	Secondary TR (N = 162)
Efficacy			
Acute procedural success[e]	Acute phase	100.0%	96.9%
Percentage of subjects with TR severity reduction by ≥1 grade	1 year	100.0%	96.3%
Percentage of subjects with NYHA Class I or II		100.0%	82.7%
Re-intervention for TR		0.0%	4.3%
Percentage of subjects with KCCQ score improvement of ≥10 points		88.9%	54.0%
Safety			
All-cause mortality	1 year	0.0%	9.3%
Device embolism		0.0%	0.0%
Incidence of SLDA		0.0%	7.4%
Tricuspid valve stenosis		0.0%	4.3%

Table 43 presents the results of efficacy and safety evaluation in the single-arm cohort of the US pivotal study. The results of primary TR were favorable as in the randomized cohort.

Table 43. Efficacy and safety results by TR etiology (single-arm cohort)

Item	Time point	Incidence (%)	
		Primary TR (N = 9)	Secondary TR (N = 85)
Efficacy			
Acute procedural success	Acute phase	100.0%	97.6%
Percentage of subjects with TR severity reduction by ≥1 grade	1 year	100.0%	100.0%
Percentage of subjects with NYHA Class I or II		88.9%	81.3%
Re-intervention for TR		11.1%	8.2%
Percentage of subjects with KCCQ score improvement of ≥10 points		44.4%	55.6%
Safety			
All-cause mortality	1 year	0.0%	17.6%
Cardiac failure hospitalization		0.0%	27.1%
Tricuspid valve surgery		0.0%	2.4%
Device embolism		0.0%	0.0%
Incidence of SLDA		0.0%	10.6%
Tricuspid valve stenosis		0.0%	2.4%

The results of the subgroup analysis demonstrated the efficacy and safety of the TriClip, regardless of primary or secondary TR etiology. Both primary and secondary TR should be included in the indication of the TriClip.

PMDA's view:

The Japanese clinical study did not enroll subjects with primary TR, while the US pivotal study enrolled a small number of subjects with primary TR. The results of the subgroup analysis showed no particular issue. Currently, only limited treatment options are available for patients with primary or secondary TR who are eligible for the TriClip therapy. Primary TR, which results from a change in the tricuspid valve leaflet and subvalvular tissue itself, is expected to benefit from intervention with the TriClip. Taken together, and taking into consideration the results of the subgroup analysis and the comments from the Expert Discussion, both primary and secondary TR should be included in the indication.

[e] Definition of acute procedural success: Clip placement was successful with TR severity reduction by ≥1 grade as assessed by the ECL based on echocardiographic data at discharge (if echocardiographic data at discharge are not available or evaluable, data at 30 days post-procedure can be used). Death or tricuspid valve surgery prior to discharge does not constitute a procedural success.

6.B.(3) Specific risks of the TriClip

6.B.(3).1) Procedural learning curve

PMDA asked the applicant to explain the learning curve of the procedure for transcatheter tricuspid valve repair with the TriClip, which is a MitraClip-based product that has been modified for TR treatment, based on the results of each clinical study, including those in the Roll-in cohort.

The applicant's explanation:

Table 44 presents learning curve assessment in the US pivotal study and the Japanese clinical study.

Table 44. Learning curve assessment

Item	US pivotal study			Japanese clinical study	
	Roll-in cohort (N = 141)	Randomized cohort Early stage, TriClip (N = 172)	Randomized cohort Late stage, TriClip (N = 109)	Roll-in (N = 19)	Primary analysis (N = 37)
Total procedure time	185 min	151 min	141 min	204 min	184 min
Clip placement time	112 min	90 min	79 min	137 min	115 min
Acute procedural success	78%	89%	95%	100%	100%
Procedure- or device-related mortality at 30 days post-procedure	0.7%	0%	0%	0%	0%
Major breeding at 30 days post-procedure	7.1%	5.2%	0%	5.3%	5.4%
Incidence of SLDA at 12 months post-procedure	9.9%	7.0%	2.8%	10.5%	5.4%
TR severity reduction to moderate or less at 30 days post-procedure	68%	87%	92%	84%	80%

Both the US pivotal study and the Japanese clinical study demonstrated a shorter procedure time and a lower incidence of SLDA in the analysis cohort than those in the Roll-in cohort. In the Japanese clinical study, the primary analysis cohort had a smaller percentage of subjects with TR severity reduction to moderate or less at 30 days post-procedure than that in the Roll-in cohort, which was likely due to a difference in the percentage of subjects with Grade 5 TR at baseline (68.2% in the Roll-in cohort, 78.4% in the primary analysis cohort). The Japanese clinical study revealed comparable procedure- or device-related adverse events in both cohorts.

In the Japanese clinical study, the median number of subjects enrolled at each study site was 4 and the sample size per site was limited. However, the results of the US pivotal study demonstrated a learning curve of the procedure with the TriClip.

PMDA's view:

Because of the characteristics of the TriClip, residual TR cannot be fully prevented. In the event of SLDA, additional measures, including the additional placement of the TriClip and surgery, are required. Therefore, these risks must be minimized as much as possible. Since a learning curve of the procedure with the TriClip exists, the applicant should implement measures that minimize the effect of the learning curve, such as developing systems for training programs and technical support. The appropriateness of the post-marketing safety measures is discussed later in Section "6.B.(5) Post-marketing safety measures."

6.B.(3).2) Effect on post-procedural treatment

The applicant's explanation about the potential effect of the TriClip device on treatments, such as tricuspid valve surgery, cardiac pacemaker placement, and right cardiac catheterization, which may be performed after the TriClip placement:

To date, the following procedures after the TriClip placement were reported without particular problem: Tricuspid valve surgery (tricuspid valve replacement in 13 subjects, tricuspid annuloplasty in 2 subjects, and endoscopic tricuspid valve repair in 1 subject in the US pivotal study; and tricuspid valve replacement in 1 subject in the Feasibility study) and cardiac pacemaker implantation (30 subjects in the US pivotal study and 2 subjects in the Feasibility study). Information on right cardiac catheterization was not collected in those studies. No new risk was identified for tricuspid valve surgery or implantation of a new cardiac pacemaker. The leads passed through the tricuspid valve during pacemaker implantation without any problem, suggesting that the TriClip implanted is unlikely to affect right cardiac catheterization.

PMDA's view:

No particular issues during procedures after the TriClip placement have been reported to date. Nevertheless, it should be noted that valve replacement will be the main tricuspid valve surgical option because of the potential influence of the TriClip. In addition, the applicant should periodically analyze the long-term outcome of the clinical studies and other data, provide information to healthcare professionals as well as take risk reduction measures, as necessary.

6.B.(3).3) Placement of multiple clips

In the clinical studies, the index procedure was completed in many subjects after 2 clips were placed. Some subjects received up to 4 clips. PMDA asked the applicant to explain the risk for placement of multiple TriClip devices.

The applicant's explanation:

In the Feasibility study, a majority of subjects received 2 (47.1%) or 3 (28.2%) clips and the maximum number of clips implanted was 4 (4.7%). In view of these findings, placement of additional clips, up to 4 clips in principle, was permitted in the US pivotal study and the Japanese clinical study in the case that the first clip placement failed to provide satisfactory TR severity reduction.

The US pivotal study showed that the mean transtricuspid pressure gradient was maintained at <5 mmHg through 12 months post-procedure in the randomized cohort (except for 10 of 172 subjects), which was approximately 1 mmHg higher than that in the control cohort. Subjects with a mean transtricuspid pressure gradient of ≥5 mmHg had no clinically significant symptoms and required no additional intervention, etc. Figure 28 presents the relationship between the number of clips and the transtricuspid pressure gradient at 30 days post-procedure. No correlation was observed at 30 days post-procedure or at 12 months post-procedure. The US pivotal study revealed no valve leaflet injury or tricuspid valve stenosis associated with placement of multiple clips, suggesting no clinically significant risk.

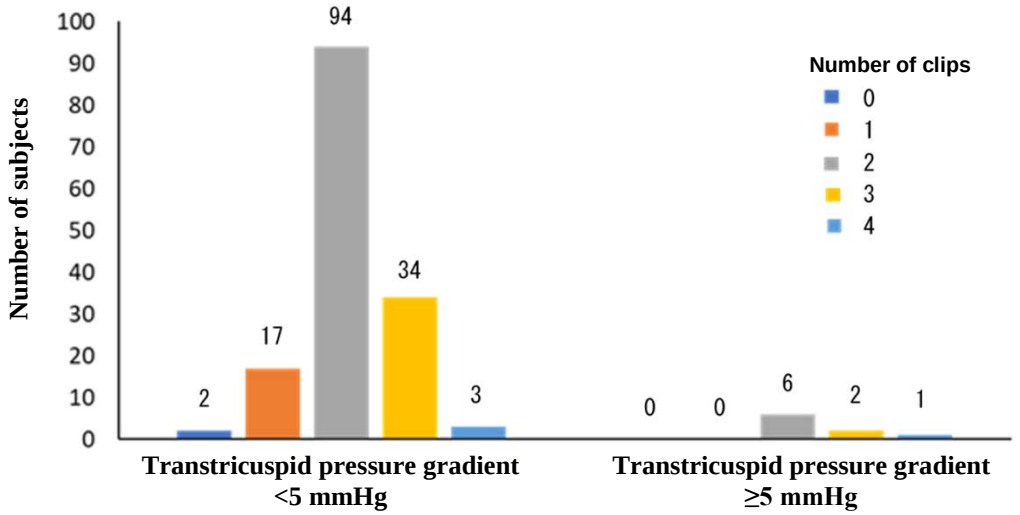


Figure 28. Relationship between the number of clips and the transtricuspid pressure gradient at 30 days post-procedure
(TriClip group in the randomized cohort of the US pivotal study)

PMDA considers that the applicant's explanation is acceptable. The clinical studies assessed the outcomes of placing up to 4 clips, but did not evaluate the efficacy and safety of using more than 4 clips. PMDA instructed the applicant to provide this information through the Information on Precautions etc. The applicant agreed to the instruction.

6.B.(4) Patients eligible for the TriClip therapy

6.B.(4).1) Clinical positioning and patients eligible for the TriClip therapy

PMDA's view:

The TriClip is indicated for use in patients with symptomatic severe TR whose severity and symptoms persist despite optimal medical therapy and for whom tricuspid valve surgery is not optimal, as determined by a heart team. This clinical positioning of the TriClip proposed by the applicant is appropriate since currently no effective treatment option is available for this patient population. It is of clinical significance to make the TriClip available in clinical practice.

However, there is no sufficient consensus on the criteria and optimal timing of surgery for the treatment of severe TR. Delayed surgical intervention for the treatment of severe TR is known to lead to irreversible impairment of right cardiac function, as well as hepatic impairment and renal impairment associated with right cardiac failure, and deterioration of systemic condition, such as cachexia, resulting in poor prognosis. Experiences with transcatheter heart valve treatment, mainly of the aortic valves and mitral valves, have also been accumulated in Japan. However, not much historical data on conventional medical and surgical treatment of tricuspid valve diseases are available compared with the above left heart diseases. In patient selection, therefore, inter-institutional variability in judgment by heart teams is anticipated.

Given this, PMDA asked the applicant about measures to ensure the selection of patients eligible for the TriClip therapy and its proper use.

The applicant's explanation:
The TriClip is indicated for use in "patients with symptomatic severe TR despite optimal medical therapy for whom tricuspid valve surgery is not optimal." The intended patient population include the following patients:

- Patients for whom tricuspid valve surgery is not optimal because of age, frailty, prior sternotomy, or other patient characteristics
- Patients in whom transcatheter edge-to-edge tricuspid valvuloplasty is clinically appropriate

Table 45 presents the reasons why the site heart teams judged that tricuspid valve surgery was not optimal for subjects in the Japanese clinical study. The most common reasons were age and frailty.

Table 45. Reasons for risks of tricuspid valve surgery as judged by site heart teams in the Japanese clinical study

Reason for the judgment that tricuspid valve surgery was not optimal	Proportion of subjects (% [N])	
	Primary analysis (N = 37)	Roll-in (N = 19)
Age and frailty	83.7% (31)	63.2% (12)
Repeat sternotomy	8.1% (3)	15.8% (3)
Prior mitral valve intervention	5.4% (2)	0% (0)
Respiratory function	2.7% (1)	5.3% (1)
Risk of haemorrhage	0.0% (0)	5.3% (1)
Severe right atrial failure	0.0% (0)	5.3% (1)

The US pivotal study enrolled patients who were at intermediate or greater estimated risk for mortality with tricuspid valve surgery, as determined by site heart teams. However, no record on the process of the patient's eligibility assessment was collected. A comparison of the characteristics of the patients enrolled in both studies revealed that geriatric patients (approximately 80 years of age) with multiple comorbidities (e.g., renal disease, hypertension, and atrial fibrillation) and a prior intervention for aortic or mitral valve disease were enrolled in these studies, suggesting that the site heart teams appropriately assessed the eligibility of each subject who was at a high risk for tricuspid valve surgery, which made tricuspid valve surgery not optimal.

The TriClip is not indicated even for patients in whom transcatheter edge-to-edge tricuspid valvuloplasty is clinically appropriate if transcatheter treatment through the thigh is challenging or tricuspid valve leaflet anatomy precludes clip implantation (e.g., very large coaptation gap, Ebstein's anomaly, and severe leaflet loss). A heart team should fully discuss the patient's eligibility for the TriClip therapy based on the anatomical requirements of the TriClip and the patient's condition.

The TriClip therapy is highly innovative. To optimize its risk-benefit balance, selection of eligible patients is critical. To this end, the applicant has planned to create guidelines for proper use that define the qualifications for medical institutions and physicians for this therapy as well as patient selection criteria, in cooperation with related academic societies (the Japanese Heart Failure Society, the Japanese College of Cardiology, the Japanese Society of Echocardiography, the Japanese Association of Cardiovascular Intervention and Therapeutics, the Japanese Society for Cardiovascular Surgery, and the Japanese Circulation Society) and to establish the system that ensures the optimal use of the TriClip in eligible patients as judged by their heart teams. Table 46 presents the issues related to the indication of the TriClip in the draft guidelines for proper use proposed by the related academic societies.

Table 46. Patient selection criteria in the draft guidelines for proper use

Indication, etc.
Patients in the chronic phase (including those just out of the acute phase) who have severe tricuspid regurgitation (TR; its severity assessed either at rest or on exertion) with cardiac failure symptoms, are not optimal candidates for surgery, but have a tricuspid valve anatomy suitable for the treatment with a percutaneous tricuspid valve repair system

Patients eligible for this therapy
Patients must meet all of the criteria shown below:
- Patient has symptomatic chronic TR (TR ≥3+ at rest or on exertion) in whom TR reduction after the treatment with a percutaneous tricuspid valve repair system is expected to decrease symptoms or improve the function.
- Patients in whom left heart disease (e.g., severe mitral regurgitation and severe aortic valve stenosis) has been adequately treated according to the clinical practice guidelines for valvular disorders.
- Patients for whom surgery is not optimal. Surgical risks must be assessed by a heart team consisting of internal cardiologists and cardiovascular surgeons, including physicians specializing in cardiac failure care and certified cardiovascular surgeons.
- Patients in whom the femoral venous approach can be used.

Patients not eligible for this therapy
- Patient has some condition that prevents the insertion of a percutaneous tricuspid valve repair system through the femoral vein or has ipsilateral deep vein thrombosis.
- Patient has some valve leaflet anatomical feature that precludes device manipulation or implantation, or positioning for sufficient TR reduction. This includes the following but not limited to:
  - Calcification in the leaflet grasping area
  - Presence of a severe coaptation defect (>2 cm) of the tricuspid valve leaflets
  - Severe leaflet defect preventing proper clip placement
  - Epstein's anomaly (identified by having a normal annulus position while the valve leaflets are attached to the walls and septum of the right ventricle)
- Patient has an active degenerative lesion in the tricuspid valve, such as active infectious endocarditis of the tricuspid valve.
- Patient is post-artificial valve replacement in tricuspid position.
- Patient has right cardiac tumor, right intracardiac thrombosis, or right intracardiac vegetation.
- Patient has esophageal disease that precludes transesophageal echocardiography.
- Patient for whom any of the raw materials of the percutaneous tricuspid valve repair system or the drugs required for the procedure are contraindicated, or who has known hypersensitivity to any of them.
- Patient has tricuspid valve stenosis (defined as a tricuspid valve orifice area of ≤1.0 cm^2 or mean pressure gradient of ≥5 mmHg).
- Patient has systolic pulmonary artery pressure (sPAP) >70 mmHg as determined by echocardiography or fixed pre-capillary pulmonary hypertension as assessed by right heart catheterization.
- Patient is experiencing an acute exacerbation.
- Patient is dependent on cardiotonic (catecholamine) (except for its temporal use).
- Patient is on circulatory support (except for its temporal use).

PMDA's view:

The applicant's policy that ensures the proper use of the TriClip in cooperation with the related academic societies was appropriate, taking into consideration the comments from the Expert Discussion. The applicant should review the appropriateness of the patient's eligibility criteria in the post-marketing setting and jointly work with the related academic societies in order to ensure the continuous proper use of the TriClip based on evidence accumulated in the future in and outside Japan. In order to ensure that eligible patients are selected in compliance with the guidelines for proper use, PMDA instructed the applicant to include this precautionary information in the Information on Precautions etc. The applicant agreed to the instruction.

6.B.(4).2) Intended use or indication of the TriClip

Left cardiac disease, if any, must be adequately treated before the start of the TriClip therapy, considering its clinical positioning and the patient populations of the clinical studies. Taking into consideration the results of the Japanese clinical study, etc. and the comments from the Expert Discussion, PMDA concluded that the following intended use or indication of the TriClip should be included

Intended use or indication (The underlined texts denote changes.)

The TriClip System is indicated to treat tricuspid regurgitation in patients with symptomatic severe tricuspid regurgitation whose severity and symptoms persist despite optimal medical therapy and who meet all of the following criteria, as determined by a heart team.

- Patients whose left heart disease has been adequately treated in accordance with the Japanese guidelines.
- Patients for whom tricuspid valve surgery is not optimal.
- Patients in whom transcatheter edge-to-edge tricuspid valvuloplasty is clinically appropriate

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

The applicant's explanation about the post-marketing safety measures of the TriClip:

Table 47 presents the details of training programs planned to be provided in Japan. Classroom training programs and hands-on training programs to learn the procedural sequence of the TriClip will be provided to physicians. In addition, imaging procedures are essential in the TriClip therapy to capture adequate images of the tricuspid valve as its structure is more complicated than the other valves. Therefore, training for imaging will be provided to echocardiography physicians. Company's product specialists will attend the procedures for all patients to provide technical support during the placement of the TriClip device. The marketing system in Japan, including the details of the training programs and technical support, will be the same as that in the US.

Table 47. Overview of the training programs

	Training	Details	Trainee
1	Introduction	Classroom lectures on pathology, eligible patients, target disease, etc.	Heart team members
2	Basic training	Classroom lectures and hands-on training on the basic performance of the TriClip, preparation/operation methods, TEE image during procedure, and troubleshooting (from preparation to removal of the TriClip)	Treating physicians and echocardiography physicians
3	Patient screening (classroom lecture)	Anatomical assessment of the tricuspid valve by TTE/TEE in actual patients and learning on how to create surgical strategy	Treating physicians and echocardiography physicians (optional for non-physician healthcare professionals)
4	Patient screening (attending the procedure)	Attending actual examination to learn patient screening by clinical specialists or echocardiography physicians and learning on how to create surgical strategy	Echocardiography physicians (optional for treating physicians and non-physician healthcare professionals)
5	Hands-on (dry run)	Hands-on training using a demo and a mock heart (from preparation to removal of the TriClip)	Treating physicians and non-physician healthcare professionals

The related academic societies are drafting the qualifications for medical institutions and treating physicians for the TriClip therapy, which are presented in Table 48. In addition to team composition, medical institutions and treating physicians must have some experience in transcatheter mitral valve repair. The TriClip will be introduced to Japan after its safety is assured.

Table 48. Draft qualifications for medical institutions and treating physicians

Item	Details
Qualifications for medical institutions	This is team-based treatment. It should not be performed by a specific physician alone. A team can consist of physicians specializing in each field of intervention, cardiac ultrasonography, cardiac failure management, and cardiovascular surgery. Medical institutions are required to have facilities and experience that ensure the safe performance of the procedure with a percutaneous tricuspid valve repair system. • Medical institution is certified for Mitral Transcatheter Edge-To-Edge Repair (M-TEER). • Medical institution in which M-TEER has been performed in at least 12 patients in the last 1 year. • Medical institution in which M-TEER has been performed in at least 50 patients.
Qualifications for treating physicians	• Treating physician has completed the training programs for the TriClip device. • Treating physician has attended the procedure using the TriClip device in at least 1 patient. <u>Implanting physicians</u> • Implanting physician has performed M-TEER in at least 50 patients as the primary surgeon. <u>Echocardiography physicians</u> • Echocardiography physician is a physician specializing in echocardiogram who is fully or provisionally certified by the Japanese Society of Echocardiography or board-certified echocardiographer for SHD, or has passed a qualification test of the Japanese Board of Perioperative Transesophageal Echocardiography (JB-POT). • Echocardiography physician has performed transesophageal echocardiography for M-TEER in at least 50 patients.

PMDA's view:

A multidisciplinary heart team should select eligible patients and use the TriClip after receiving adequate training on the TriClip therapy at medical institutions capable of treating various complications in order to optimize the risk-benefit balance of the TriClip. Taking into consideration the comments from the Expert Discussion, the following measures proposed by the applicant were appropriate: The training programs and technical support to be provided by the applicant, as well as the post-marketing safety measures, including the qualification for medical institutions and treating physicians created in cooperation with the related academic societies. These should be included as Approval Condition 1.

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

7.A Summary of the data submitted

Table 49 presents a summary of the planned use-results survey (draft) of the TriClip.

Table 49. Summary of the planned use-results survey (draft)

Item	Summary
Objective	To evaluate the efficacy and safety of the TriClip in post-marketing clinical practice
Target sample size	All patients (up to 250) Rationale Key survey items are SLDA, a specific risk of the TriClip, and TR severity reduction as an efficacy endpoint. The sample size was determined based on the estimations shown below: • Assuming that the performance goal for the incidence of SLDA at 30 days post-procedure is 8.8% based on the results of the clinical studies of the TriClip and that the incidence in this survey is 4%, the sample size of 250 ensures a power of >90% at a one-sided significance level of 5%. • Assuming that the performance goal for the percentage of patients with TR severity reduction to moderate or less at 30 days post-procedure is 71% based on the results of the clinical studies of the TriClip and that the incidence in this survey is 80%, the sample size of 250, as with SLDA, ensures a power of >90% at a one-sided significance level of 5%.
Survey period	6 years (preparation, 6 months; patient registration, 2 years; follow-up, 3 years; analysis, 6 months)
Key survey items	• Incidence of SLDA at 30 days post-procedure (the incidence in the early and late stages will also be analyzed to assess a learning curve) • TR severity reduction to moderate or less at 30 days post-procedure
Other survey items	• Patient characteristics and procedural information • Follow-up information (e.g., TTE, NYHA Class, KCCQ score, 6-minute walk distance, information on medication, and blood sampling) • Adverse events, deaths, and device malfunctions • Cardiac failure hospitalization

7.B Outline of the review conducted by PMDA

PMDA's view:

The applicant should collect the efficacy and safety data of the TriClip, which will be the first medical device approved in Japan for transcatheter TR treatment, through a post-marketing surveillance, etc. and take additional measures for risk reduction and proper use in a timely manner as necessary.

The proposed key survey items and sample size are appropriate to assess the sufficiency of the proposed post-marketing safety measures and the necessity of additional risk reduction measures because the US pivotal study and the Japanese clinical study demonstrated a learning curve of the procedure with the TriClip. PMDA concluded that it is reasonable to enroll all patients in the use-results survey since transcatheter TR treatment is highly innovative and procedural outcome has a substantial impact on therapeutic outcome. On the basis of the results of the clinical studies submitted, the other survey items are also adequate for the safety and efficacy evaluation of the TriClip.

PMDA asked the applicant to explain the appropriateness of the 3-year follow-up period.

The applicant's explanation:

Device- and procedure-related complications, including SLDA, tended to occur in the early post-procedure stage. Such complications are not expected to increase after 3 years post-procedure. In addition, the Feasibility study demonstrated the 3-year efficacy, with TR severity reduction, and KCCQ score and NYHA Class improvement, as well as long-term safety, suggesting the appropriateness of the 3-year follow-up period.

PMDA's view:

The applicant's explanation is generally reasonable and the proposed follow-up period is acceptable because (i) the applicant has planned to report the long-term outcome of the TriClip therapy based on

the results of analyses of long-term outcome data from the submitted clinical study results and (ii) the Japanese clinical study revealed no risks specific to Japanese subjects.

Taking into consideration the comments from the Expert Discussion, PMDA concluded that the draft survey plan proposed by the applicant is appropriate and that the conduct of this survey should be imposed as Approval Condition 2.

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

8.A Summary of the data submitted

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

8.B Outline of the review conducted by PMDA

On the basis of the conclusion of the Expert Discussion, PMDA concluded that there were no particular problems with the proposed Information on Precautions, etc., provided that the applicant advises necessary precautions.

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

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

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

IV. Overall Evaluation

PMDA's review of the application for the TriClip System primarily focused on (1) the efficacy and safety of the TriClip System and (2) post-marketing safety measures, including selection of eligible patients. On the basis of the comments from the Expert Discussion, PMDA reached the following conclusions:

(1) Efficacy and safety of the TriClip

The foreign clinical study results demonstrated that the interventional treatment with the TriClip reduced TR severity and improved KCCQ score and NYHA Class in subjects with symptomatic severe TR who did not respond to optimal medical therapy and were not optimal candidates for surgery, as determined by heart teams. The Japanese clinical study also showed TR severity reduction with a low incidence of procedural complications, as seen in the foreign clinical study. The randomized cohort of the US pivotal study achieved the primary endpoint, to which QOL improvement mainly contributed. There was no

difference in the hard endpoints including mortality between the TriClip and control groups. The results did not show that the TriClip System reduced TR severity to improve the prognosis of subjects. However, the study revealed no noteworthy safety events related to the TriClip System. Currently, no effective therapy is available for patients with symptomatic severe TR for whom tricuspid valve surgery is not optimal despite optimal medical therapy. Given this, PMDA concluded that the risk-benefit balance of the TriClip System could be ensured in appropriately selected eligible patients.

(2) Post-marketing safety measures, including selection of eligible patients

To ensure the effective and safe use of the TriClip System in Japan, users who have adequate knowledge and experience in symptomatic severe TR must acquire knowledge and skills required for the procedures of the TriClip therapy through training programs, etc., and a heart team must determine whether the patient should be treated with a conventional therapy (medical or surgical therapy) or the TriClip therapy, based on a thorough understanding of the characteristics of the TriClip therapy. In addition, complications associated with the use of the TriClip System or the placement procedures must be treated appropriately. To treat patients with symptomatic severe TR, TriClip System should be used by physicians with sufficient experience in medical and surgical treatment of symptomatic severe TR and capability of appropriately treating such complications at medical institutions with a well-established system for the treatment (Approval Condition 1). Since the TriClip System will be the first medical device for transcatheter TR treatment introduced into Japan, information regarding the procedural success rate, the incidence of adverse events, and efficacy should be collected after its launch in Japan through a post-marketing surveillance, etc., and additional risk reduction measures should also be taken as necessary (Approval Condition 2). The use-results survey period for the TriClip Sytem should be 6 years (preparation, 6 months; registration, 2 years; follow-up, 3 years; analysis, 6 months). Annual reports from the submitted clinical studies should be submitted to assess the long-term outcome of the TriClip therapy (Approval Condition 3).

As a result of the above review, PMDA has concluded that the TriClip System may be approved for the intended use modified as shown below, with the following approval conditions.

Intended Use or Indication

The TriClip System is indicated to treat tricuspid regurgitation in patients with symptomatic severe tricuspid regurgitation whose severity and symptoms persist despite optimal medical therapy and who meet all of the following criteria, as determined by a heart team:

- Patients whose left heart disease has been adequately treated in accordance with the Japanese guidelines.
- Patients for whom tricuspid valve surgery is not optimal.
- Patients in whom transcatheter edge-to-edge tricuspid valvuloplasty is clinically appropriate

Approval Conditions

1. The applicant is required to take necessary measures, such as dissemination of the guidelines for proper use prepared in cooperation with related academic societies and provision of seminars, to ensure that physicians with adequate knowledge and experience in the treatment of symptomatic severe tricuspid regurgitation acquire skills for using the product and knowledge about

complications associated with the procedures and identify patients eligible for treatment and that the physicians use the product at medical institutions with a well-established system for the treatment.

2. The applicant is required to conduct a post-marketing surveillance involving all patients treated with the product until data have been accrued from a specified number of patients, to submit annual reports on the results of analyses of long-term outcomes to the Pharmaceuticals and Medical Devices Agency, and to take appropriate measures as necessary.
3. The applicant is required to submit reports on the results of analyses of long-term outcome data from participants in the clinical studies included in the present application to the Pharmaceuticals and Medical Devices Agency, and to take appropriate measures as necessary.

The product is not classified as a biological product or a specified biological product. The product is designated as a specified medical device, and its location should be identified.

The product is designated as a medical device subject to a use-results survey. The use-results survey period is 6 years.

PMDA has concluded that the present application should undergo deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

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