September 29, 2017

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

Report on the Deliberation Results

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Percutaneous repair system for mitral valve coaptation failure (to be newly created)
Brand Name	MitraClip NT System
Applicant	Abbott Vascular Japan Co., Ltd.
Date of Application	October 28, 2016 (Application for marketing approval)

Results of Deliberation

In its meeting held on September 29, 2017, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

The period of use-results survey should be 6 years.

Approval Conditions

1. The applicant is required to take necessary measures, such as dissemination of the guideline for proper use developed in cooperation with related academic societies and provision of training programs, to ensure that physicians with adequate knowledge and experience in treating symptomatic severe mitral regurgitation in high-surgical-risk patients acquire sufficient skills for using the product and knowledge about procedure-related complications, and that the product is used in accordance with the intended use and directions for use of the product at medical institutions appropriately equipped to treat the disease.
2. The applicant is required to conduct a post-marketing use-results survey involving all patients treated with the product until data from a specified number of patients have been gathered, to submit annual reports on the results of analyses of long-term outcomes to the Pharmaceuticals and Medical Devices Agency (PMDA), and to take appropriate measures as necessary.
3. The applicant is required to submit annual reports on the results of analyses of long-term outcome data from participants in the clinical studies for regulatory submission to PMDA and to take appropriate measures as necessary.

Review Report

September 12, 2017
Pharmaceuticals and Medical Devices Agency

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

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Percutaneous repair system for mitral valve coaptation failure (to be newly created)
Brand Name	MitraClip NT System
Applicant	Abbott Vascular Japan Co., Ltd.
Date of Application	October 28, 2016
Items Warranting Special Mention	Priority review
Reviewing Office	Office of Medical Devices III

Review Results

September 12, 2017

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Percutaneous repair system for mitral valve coaptation failure (to be newly created)
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Items Warranting Special Mention	Priority review

Results of Review

The MitraClip NT System was developed for the transcatheter treatment of mitral regurgitation (MR) in patients with symptomatic severe MR who are at high risk for open-heart surgery. The MitraClip NT System consists of the Clip Delivery System (CDS) equipped with a clip, Steerable Guide Catheter that delivers the CDS into the left atrium, a Dilator, and accessories (Stabilizer, Lift, and Support Plate) to support the positioning of the above components.

The applicant submitted non-clinical data supporting the physicochemical properties, biological safety, stability and durability, performance, and directions for use. PMDA reviewed the submitted data and identified no particular problem.

To support the clinical evaluation of the MitraClip NT System, the applicant submitted the results of a foreign clinical study "EVEREST II RCT study" that compared the MitraClip NT System and surgery in non-high-surgical-risk patients, foreign clinical studies "EVEREST II High Risk Registry" and "EVEREST II REALISM Continued Access Study High Risk Cohort" in high-surgical-risk patients with severe MR, an integrated data analysis combining the results of these 2 studies "Integrated High Risk Cohort," and a Japanese clinical study "Study AVJ-514." As reference data, the applicant submitted the results from the "EVEREST II Roll-In study" and the "Realism Non-HR study."

Because of differences in etiology between degenerative MR and functional MR, the efficacy and safety of the MitraClip NT System were evaluated separately for each etiology, based on the results from the Integrated High Risk Cohort consisting of high-surgical-risk patients with severe MR (severity 3+/4+).

The Integrated High Risk Cohort included 105 high-surgical-risk patients with symptomatic degenerative MR. Acute procedural success was defined as the successful implantation of the MitraClip NT Device with MR severity ≤2+ at discharge. In this cohort, acute procedural success was achieved in 79.0% (83 of 105) of patients, and MR severity ≤2+ was achieved in 85.3% (58 of 68) of

patients at 12 months. The proportion of patients with New York Heart Association (NYHA) Functional Class ≤II increased from 18.1% (19 of 105 patients) at baseline to 87.3% (62 of 71 patients) at 12 months. The rate of hospitalization for cardiac failure per patient-year also improved from 0.68 to 0.18 after the procedure. The Duke University's database for existing data from patients receiving medical therapy was used to compare the risk for interventional treatment with the MitraClip NT System with that for medical therapy. A total of 953 patients with symptomatic MR deemed high risk for surgery were extracted from the Duke University database including [redacted] patients (DUKE Data). Further, the data were propensity score matched to extract 65 patients with degenerative MR for comparison. The mortality at 12 months was 20.0% in the MitraClip group and 30.6% in the DUKE group. The hazard ratio for the risk of death at 12 months in the MitraClip group was 0.63 (95% confidence interval [CI], 0.25-1.61), showing no difference in the hazard ratio. The MitraClip NT System is intended to be used in high-surgical-risk patients. In addition, no effective treatment is available to improve MR as the primary disease. Given this, the MitraClip NT System is effective in the treatment of degenerative MR, and its benefits overweigh its risks.

The proportion of high-surgical-risk patients with symptomatic functional MR who had acute procedural success was 85.0% (209 of 246 patients), with MR severity ≤2+ at 12 months in 82.8% (130 of 157 patients). The proportion of patients with NYHA Functional Class ≤II increased from 13.8% (34 of 246 patients) at baseline to 81.0% (132 of 163 patients) at 12 months. The rate of hospitalization for cardiac failure per patient-year also improved from 0.81 to 0.39 after the procedure. A comparison between 246 patients in Integrated High Risk Cohort and another 246 patients selected by propensity score matching from the DUKE Data showed that mortality at 12 months was 21.9% in the MitraClip group and 34.3% in the DUKE group. The hazard ratio for the risk of death at 12 months in the MitraClip group was 0.56 (95% CI, 0.38-0.82), showing a significantly lower hazard ratio for the risk of death in the MitraClip group than in the medical therapy group. This result suggested that the MitraClip NT System was associated with a lower mortality. Patients with symptomatic functional MR have a poor outcomes despite adequate treatments including optimal medical therapy for the primary disease. In addition, there is no effective treatment available for high-surgical-risk patients. For these reasons, PMDA concluded that the benefits of the MitraClip NT procedure outweighed its risks.

On the other hand, although the MitraClip NT System can provide a minimally invasive therapy to reduce MR, the therapy is unavoidably associated with a certain risk of procedural failure attributable to its characteristics and procedural failure-related complications. To maximize the risk-benefit balance of the MitraClip NT System in the target patient population, it is crucial for physicians to fully understand the characteristics of the MitraClip NT procedure and then to decide whether to use it after considering conventional medical therapies and surgery. Since complications related to the MitraClip NT System or to the procedure need to be treated appropriately, the MitraClip NT System must be used by physicians who have sufficient experience and capability of performing medical and surgical treatments of severe cardiac failure in patients with severe MR at medical institutions well-equipped to treat such patients.

The results of Study AVJ-514 were consistent with those of the foreign clinical studies. However, this study involved only a limited number of patients. The MitraClip NT System will be the first medical device approved for the transcatheter treatment of MR in Japan. Information regarding the MitraClip NT procedure, including procedural success rate and incidence of adverse events, in the post-marketing setting in Japan must be collected through a use-results survey. Additional risk mitigation measures should also be taken as necessary. Since there are only limited data on the long-term outcome of the MitraClip NT procedure in and outside Japan, the applicant is required to submit the annual follow-up reports from the submitted clinical studies in order to assess the long-term outcome of the MitraClip NT procedure.

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

Intended Use

Treatment of mitral regurgitation in patients with symptomatic severe mitral regurgitation (MR severity 3+ or 4+) with a left ventricular ejection fraction of ≥30% who are at high risk for open-heart surgery, except for patients who:

- Have functional mitral regurgitation that has not been adequately treated with optimal medical therapy recommended by Japanese guidelines,
- are experiencing acute worsening,
- have dependence on inotropic drugs (catecholamine), or
- are using assisted circulation.

Approval Conditions

1. The applicant is required to take necessary measures, such as dissemination of the guideline for proper use developed in cooperation with related academic societies and provision of training programs, to ensure that physicians with adequate knowledge and experience in treating symptomatic severe mitral regurgitation in high-surgical-risk patients acquire sufficient skills for using the product and knowledge about procedure-related complications, and that the product is used in accordance with the intended use and instructions for use of the product at medical institutions appropriately equipped to treat the disease.
2. The applicant is required to conduct a post-marketing use-results survey involving all patients treated with the product until data from a specified number of patients have been gathered, to submit annual reports on the results of analyses of long-term outcomes to the Pharmaceuticals and Medical Devices Agency (PMDA), and to take appropriate measures as necessary.
3. The applicant is required to submit annual reports on the results of analyses of long-term outcome data from participants in the clinical studies for regulatory submission to PMDA and to take appropriate measures as necessary.

Review Report

September 12, 2017

Product for Review

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Term Name	Percutaneous repair system for mitral valve coaptation failure (to be newly created)
Brand Name	MitraClip NT System
Applicant	Abbott Vascular Japan Co., Ltd.
Date of Application	October 28, 2016
Proposed Intended Use	Treatment of mitral regurgitation in patients with symptomatic severe mitral regurgitation (MR severity 3+ or 4+) with a left ventricular ejection fraction of ≥30% who are at high risk for open-heart surgery
Items Warranting Special Mention	Priority review

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List of Abbreviations

ACC	American College of Cardiology
ACE	Angiotensin-Converting-Enzyme
AHA	American Heart Association
ARB	Angiotensin II Receptor Blocker
ASTM	American Society for Testing and Materials
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CDS	Clip Delivery System
CEC	Clinical Events Committee
COPD	Chronic Obstructive Pulmonary Disease
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy Defibrillator
ECL	Echocardiography Core Laboratory
FDA	Food and Drug Administration
IABP	Intra-Aortic Balloon Pumping
ICD	Implantable Cardioverter Defibrillator
ITT	Intent to Treat
LVEDD	Left Ventricular End Diastolic Dimension
LVEDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESD	Left Ventricular End Systolic Dimension
LVESV	Left Ventricular End Systolic Volume
LVIDd	Left Ventricular Internal Diameter - diastolic
LVIDs	Left Ventricular Internal Diameter - systolic
MCS	Mental Component Score
MI	Myocardial Infarction
MR	Mitral regurgitation
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PCS	Physical Component Score
PP	Per Protocol
QOL	Quality of Life
RCT	Randomized Controlled Trial
RNT	Randomized Not Treated
SEM	Scanning Electron Microscope
SGC	Steerable Guide Catheter
STS	Society of Thoracic Surgeons
TEE	Transesophageal Echocardiogram
TTE	Transthoracic Echocardiogram

I. Product Overview

The MitraClip NT System consists of the Clip Delivery System (CDS) (Figure 2) equipped with a clip (Figure 1), Steerable Guide Catheter (SGC) (Figure 3) that delivers the CDS into the left atrium, a Dilator, and accessories (Stabilizer, Lift, and Support Plate) to support the positioning of these components. Regurgitation from a mitral valve can be reduced by coapting the anterior and posterior leaflets of the mitral valve with the clip inserted percutaneously (Figure 4).

Figure 1. Exterior appearance of clip

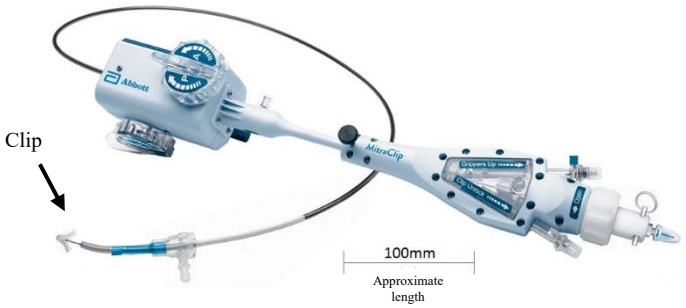


Figure 2. Exterior appearance of CDS

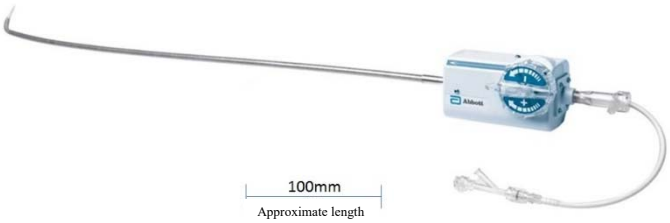


Figure 3. Exterior appearance of SGC

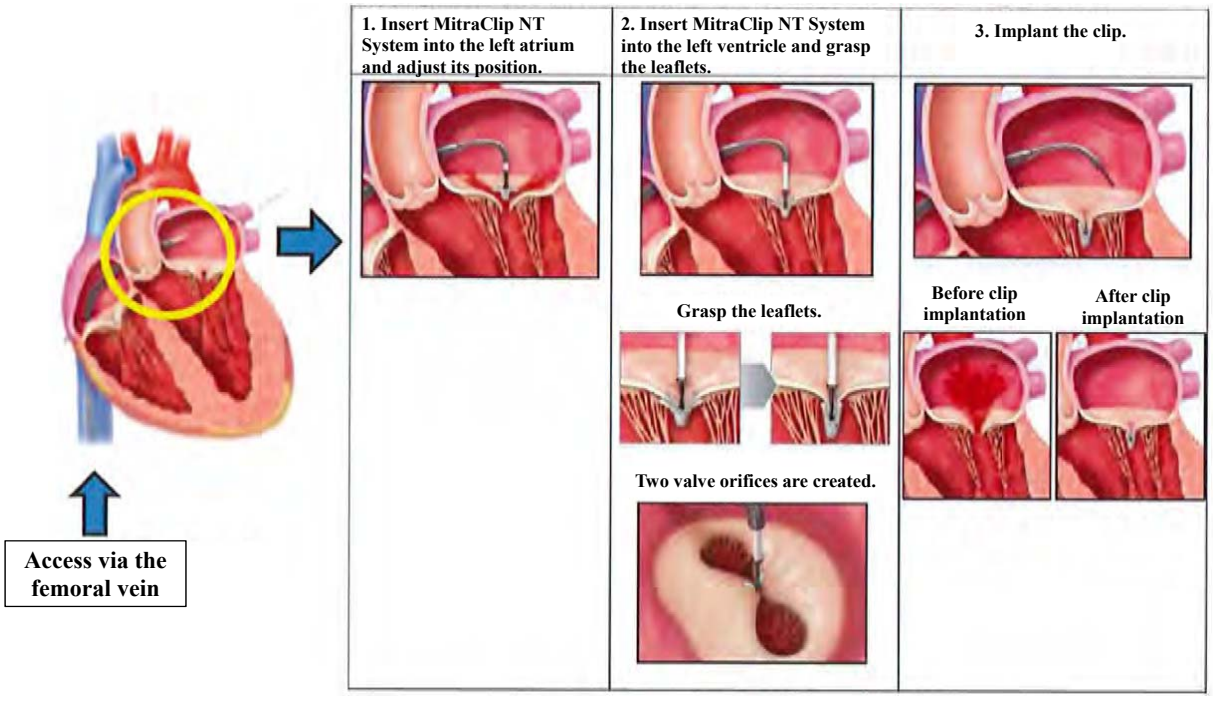


Figure 4. Treatment procedure

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

The data submitted for the present application by the applicant 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 MitraClip NT System declared that they did not fall under Item 5 of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA administrative Rule No. 8/2008 dated December 25, 2008).

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

1.A Summary of the data submitted

1.A.(1) History of development

In the United State (US), 250,000 patients are newly diagnosed with mitral regurgitation (MR) each year. Its prevalence is higher than that of aortic, pulmonary arterial, or mitral valve disease. MR accounts for approximately 70% of valve disease cases.

MR is pathophysiologically classified into either primary or secondary MR. Primary MR, which is also called degenerative MR, results from poor leaflet coaptation that is caused by an organic abnormality of the valve tissue due to myxomatous degeneration, elastic fiber dysfunction, and other structural abnormalities. Secondary or functional MR, on the other hand, occurs when a structurally normal mitral valve fails to fully close because the leaflets are pulled toward the ventricle due to left ventricular dysfunction, such as left ventricular enlargement associated with ischemic cardiomyopathy (e.g., coronary artery disease) or non-ischemic cardiomyopathy (e.g., dilated cardiomyopathy). Both types of MR are associated with poor coaptation of the mitral valve leaflets, which causes regurgitation, resulting in volume overload. In the early stage of MR, cardiac output can be maintained by the compensatory mechanism of the heart. However, a long-term compensatory rise in heart rate may contribute to left ventricular enlargement (left ventricular remodeling), which results in progressive left ventricular dysfunction, causing symptoms of cardiac failure.

Asymptomatic, mild to moderate MR is only followed without particular treatment. Once symptoms appear because of left ventricular dysfunction, however, medical pharmacotherapy or surgery (valvuloplasty or valve replacement) is considered to treat cardiac failure. Surgery can be curative, but it requires a heart-lung machine to stop the heart. The surgical procedure is highly invasive and is associated with the risk of death or severe disabilities due to procedure-related complications. Medical therapy may be continued in patients at a high risk for surgery because of old age or prior thoracotomy.

Evalve Inc., US (currently Abbott Vascular Inc., US) developed the MitraClip NT System as an alternative treatment to cardiac surgery involving thoracotomy or continued medical therapy. The MitraClip NT System enables percutaneous treatment of MR under beating-heart conditions. The MitraClip NT System is a medical device to reduce MR by coapting the anterior and posterior leaflets of the mitral valve with the clip inserted into the heart percutaneously. This intervention uses a

double-orifice valve configuration (edge-to-edge repair), which was established as one of surgical mitral valvuloplasty procedures.

In the 17th Meeting of the Study Group on the Early Introduction of Medical Devices, etc. with High Medical Need in 2011, the MitraClip NT System, a clip "used for mitral valvuloplasty that creates a double valve orifice to reduce MR by coapting the centers of the anterior and posterior leaflets with the clip," was designated as a medical device requiring early introduction.

During the development of the MitraClip NT System after CE mark clearance, various modifications were made to the CDS to improve its productivity and performance. Table 1 shows the history of the modifications of the MitraClip NT System.

Table 1. History of modifications of MitraClip NT System

Model	Modification from the previous model (summary)
CDS01	-
CDS02	[redacted]
CDS05 (MitraClip NT System)	

Note) CDS01 was used in the foreign clinical studies. CDS02 was used in the foreign and Japanese clinical studies.

1.A.(2) Use in foreign countries

Table 2 shows the information regarding approvals and sales performance in key foreign countries. The sales figures of the CDS are described separately for the previous model (CDS02) and current model (CDS05) of the MitraClip NT System.

Table 2. Use in key foreign countries (Surveyed in March 2017)

	Date of authorization or approval Sales performance			
	Europe	US	Others	Total
CDS01	March 4, 2008 -	- -	-	-
CDS02	November 12, 2009 [redacted]	October 24, 2013 [redacted]	[redacted]	[redacted]
CDS05 (MitraClip NT System)	December 19, 2015 [redacted]	May 10, 2016 [redacted]	[redacted]	[redacted]
SGC	March 4, 2008 [redacted]	April 27, 2009 [redacted]	[redacted]	[redacted]

Note) Survey period, July 2015 to February 2017

Table 3 shows the intended use of the MitraClip NT System in the key foreign countries.

Table 3. Intended use in key foreign countries

Europe	US
The device is intended for reconstruction of the insufficient mitral valve through tissue approximation.	The device is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.

1.A.(3) Device malfunctions reported in foreign countries

Tables 4 to 7 show common device malfunctions and adverse events (incidence ≥0.1%) reported for the MitraClip NT System in foreign countries.

Table 4. Device malfunctions reported in foreign countries (CDS05 or MitraClip NT System) (Surveyed in March 2017)

Type of device malfunctions	Number of cases	Incidence (%)
Incomplete coaptation (single leaflet device attachment)	[redacted]	0.7901
Difficulty in grasping the leaflets and coapting the devices (difficulty in adhesion to/coaptation of device parts, other devices, or the patient's body)	[redacted]	0.3523
Improper device use	[redacted]	0.3096
Difficulty in clip opening/closing	[redacted]	0.2990
Removal difficulty (resistance or obstruction felt by the surgeon during removal)	[redacted]	0.2669
Implantation difficulty (implantation difficult but successful)	[redacted]	0.2135
Device operation failure (unintended device operation)	[redacted]	0.2029
Positioning difficulty	[redacted]	0.1922
Separation of parts (unintended disconnection)	[redacted]	0.1922
Restricted device operation (restricted or interrupted movements of the clip, lock line, or gripper line)	[redacted]	0.1708
Device breakage	[redacted]	0.1602
Physical resistance (device rotation or travel interrupted)	[redacted]	0.1281
Damage caused by devices contacting each other	[redacted]	0.1281

Table 5. Device malfunctions reported in foreign countries (SGC) (Surveyed in March 2017)

Type of device malfunctions	Number of cases	Incidence (%)
Leakage, air contamination	[redacted]	0.3738
Material tear	[redacted]	0.1095
Poor connection with other devices	[redacted]	0.1095

Table 6. Adverse events reported in foreign countries (CDS05 or MitraClip NT System) (Surveyed in March 2017)

Type of adverse events	Number of cases	Incidence (%)
Additional intervention (non-surgical) (additional non-surgical treatment to repair or prevent injury)	[redacted]	0.9609
Mitral regurgitation	[redacted]	0.5872
Tissue injury (laceration or perforation of the leaflets, or rupture of the tendinous cords during procedure)	[redacted]	0.4378
Hospitalization or prolonged hospitalization	[redacted]	0.3950
Surgical intervention	[redacted]	0.1495
Remnant in body, implantation outside lesion	[redacted]	0.1388

Table 7. Adverse events reported in foreign countries (SGC) (Surveyed in March 2017)

Type of adverse events	Number of cases	Incidence (%)
Additional intervention (non-surgical)	[redacted]	0.2794
Atrial perforation	[redacted]	0.1246

1.B Outline of the review conducted by PMDA

PMDA asked the applicant to explain risk mitigation measures in relation to the reported device malfunctions.

The applicant' explanation:

These device malfunctions were not because of design problems but primarily attributable to the usage of the MitraClip NT System. The residual risk is tolerable provided that some measures, such as training of surgeons and inclusion of relevant precautions in the instructions for use, are taken.

PMDA's view:

Device malfunctions reported overseas included events related to the MitraClip NT procedure, such as single leaflet device attachment, difficulty in grasping the leaflets, difficulty in coapting the devices, improper device use, and difficulty in clip opening/closing. The device malfunctions, along with adverse events, are reviewed based on the results presented in Section "6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare" described later.

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 MitraClip NT System consist of clip performance, delivery system performance, steerable sleeve performance, clip introducer, tensile strength, torque strength, compression strength, hydrophilic coating, hemostasis valve, visibility, magnetic resonance imaging (MRI) compatibility, corrosion resistance, and fatigue resistance. The proposed performance and safety specifications for the SGC are SGC performance, tensile strength, torque strength, hydrophilic coating, hemostasis valve, and visibility. The proposed specifications for 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 asked the applicant to explain the necessity of establishing specifications for the performance of the clip to catch and grasp the leaflets and maintain the grasp with the arms closed completely because these functions are important to ensure the efficacy and safety of the MitraClip NT System.

The applicant's response:

No specifications for the force necessary for the clip to grasp the leaflets can be established as performance because the anatomical characteristics, including size and condition, of the leaflets vary among patients. The clip must open and close to grasp the leaflets and have a locking function to hold the leaflets at the grasping arm angle. To ensure these functions of the clip, the specifications for clip function and fatigue resistance are established. The condition of grasping the leaflets is checked prior

to removal of the clip from the CDS. A fatigue test verified that the clip remained locked even after applying a pulsating load equivalent to 15 years. A load was placed on the clip with the fatigue testing machine so that [redacted] lbf ([redacted] N) was applied to the test samples. This figure was calculated based on [redacted] shown below.

[redacted]

The locking function of the clip closed was verified in the acute phase by applying [redacted] lbf ([redacted] N) [redacted] as [redacted]. The results of the above tests assure the clip grasping performance.

PMDA's view

The applicant's explanation is acceptable. The data on the proposed performance and safety specifications were reviewed for the appropriateness of the tests and specification limits. There was no particular problem with these specifications.

2.(2) Tests supporting safety of the device

2.(2).1) Physicochemical properties

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

To support the physicochemical properties of the MitraClip NT System, the applicant submitted the data from a nickel ion release testing (International Organization for Standardization [ISO] 10993-15), a potentiodynamic polarization test (American Society for Testing and Materials [ASTM] F2129), a galvanic corrosion testing (ASTM F3044), and MRI compatibility testing (ASTM F2052, F2182, and F2119) for the clip which is a long-term implant.

The MRI compatibility of the MitraClip NT System was evaluated by comparison with the test results of its former model (CDS01). The only differences between the MitraClip NT System and CDS01 are [redacted]% and [redacted]%. [redacted] was evaluated based on its [redacted]. The MitraClip NT System was found to have a smaller magnetic force and less artifacts compared with CDS01, and there seemed to be few differences in temperature rise between the two models. In summary, MRI compatibility tests using 1 or 2 clips implanted verified no occurrence of stent migration or drop-off, or physiologically significant temperature rise for ≤15 minutes of MR scanning under the following conditions: Static magnetic field of ≤3 Tesla, spatial field gradient of ≤2500 Gauss/cm (25 T/m), and specific absorption rate (SAR) of 3.0 W/kg. However, MRI image artifacts were detected.

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

Because the MRI compatibility tests identified some artifacts, PMDA asked the applicant to provide users with relevant information through the instructions for use and other materials. The applicant agreed. PMDA reviewed the data on the physicochemical properties of the MitraClip NT System and concluded that there was no particular problem.

2.(2).2) Biological safety

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

The applicant submitted the results of a biological safety study of the MitraClip NT System conducted in accordance with the "Basic principles of biological safety evaluation required for marketing application for medical devices (in Japanese)" (PFSB/ELD/OMDE Notification No. 0301-20, dated March 1, 2012) and the ISO 10993 series of standards, etc.

The clip was tested for cytotoxicity, sensitization, intradermal reaction, acute systemic toxicity, sub-chronic toxicity/implantation, genotoxicity (reverse mutation, chromosome abnormality, and micronucleus), pyrogenicity, and blood compatibility (hemolysis, coagulation, and complement activity). The applicant submitted the test results showing no problem. The sub-chronic toxicity/implantation and genotoxicity studies were conducted using the former model (CDS01) as the study sample. The difference in the raw materials between CDS01 and the MitraClip NT System is changes in [redacted]. Because [redacted] is also a raw material of [redacted] of CDS01, these properties of the MitraClip NT System were assessed based on the study results of CDS01.

The CDS was tested for cytotoxicity, sensitization, intradermal reaction, acute systemic toxicity, pyrogenicity, and blood compatibility (hemolysis and coagulation). The applicant submitted the test results showing no problem. The SGC and Dilator were tested for cytotoxicity, sensitization, intradermal reaction, acute systemic toxicity, pyrogenicity, and blood compatibility (hemolysis and coagulation). The applicant submitted the test results showing no problem.

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

PMDA reviewed the data on the biological safety of the MitraClip NT System and concluded that there was no particular problem.

2.(2).3) Stability and durability

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

Since all of the raw materials of the MitraClip NT System are commonly used in medical devices, the applicant submitted a self-declaration regarding the stability of the CDS and SGC based on PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012, issued by the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare.

The applicant submitted the results of a finite element analysis and a fatigue test for the clip of the MitraClip NT System and former models (CDS01 and CDS02) for evaluation of the fatigue durability. The finite element analysis was performed to simulate a load being applied on the clip in the body in order to analyze the fatigue safety of the clip, showing a safety rate exceeding 1.0. In the fatigue test, the locking status of the test samples and any breakage of the clip parts were investigated when the clip was subjected to a total of 600 million cycles of pulsating load (simulated for 15 years) in normal saline. The test demonstrated that the clip tolerated 600 million cycles of pulsating load simulated for

15 years of cardiac cycles and remained locked, without any damage to the clip, such as clip arm dislocation that might result in device and/or component embolization.

On the basis of the above test results, the applicant explained that the clip of the MitraClip NT System has a fatigue durability of ≥15 years in clinical use.

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

PMDA reviewed the data on the stability and durability of the MitraClip NT System and concluded that there was no particular problem.

2.(3) Tests supporting performance

The applicant submitted the data from design verification, animal, and performance studies to support the performance of the MitraClip NT System.

2.(3).1) Design verification studies

2.(3).1).A Summary of the data submitted

The applicant submitted the results from the design verification studies. Multiple tests shown below were performed on the CDS (MitraClip NT System or former model [CDS01 or CDS02]), SGC, and Dilator, showing that the test samples met all of the proposed specifications or criteria. Some tests were conducted using the former models. The applicant explained that it was reasonable to use the former models because the parts of the test samples were the same as those of the MitraClip NT System or were made of the same raw materials as those used in the MitraClip NT System.

(a) CDS

Clip performance, delivery performance, steerable sleeve performance, clip introducer, tensile strength, torque strength, compression strength, hydrophilic coating, hemostasis valve, visibility, and bacterial endotoxins

(b) SGC and Dilator

SGC performance, tensile strength, torque strength, hydrophilic coating, hemostasis valve, visibility, and bacterial endotoxins

2.(3).1).B Outline of the review conducted by PMDA

PMDA reviewed the data on the design verification test of the MitraClip NT System and concluded that there was no particular problem.

2.(3).2) Animal and performance studies

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

2.(3).2).A.(a) Animal studies

To evaluate the performance, and acute and long-term safety of the MitraClip NT System, the following 3 types of studies were conducted in animals (pigs) (Table 8).

Table 8. List of animal studies

	Study	Objectives and number of test samples
i	Acute/long-term safety and performance	• Evaluation of the performance of the clip and leaflet coaptation under physiological conditions • Verification of the long-term healing response of the mitral valve leaflets Follow-up period and number of test samples: • 4 weeks (n = 3), 12 weeks (n = 9), 17 weeks (n = 1), 24 weeks (n = 6), 29 weeks (n = 1), and 52 weeks (n = 1) • 1 implant per animal
ii	Acute delivery performance and safety	• Evaluation of pushability, trackability, reactivity, and removal (The visibility of the SGC was also assessed during the operation under radiographic or echocardiographic guidance in this study.) • Evaluation of the risk of causing acute intracardiac trauma and trauma to the great blood vessels Number of test samples: • 4 pigs
iii	Safety of repeated grasping	• Verification of no damage to the mitral valve and tendinous cords after repeated grasping of the leaflets with the clip Number of test samples: • 3 pigs

i Acute and long-term safety and performance of MitraClip NT Device

The study was conducted to evaluate the acute and long-term safety and performance of the MitraClip NT Device. One clip each was implanted in 21 pigs for up to 52 weeks. The study used test samples (modification in [redacted]) before and after a modification was made to [redacted] in the development phase. The difference is [redacted]. The test samples after the modification were [redacted] in [redacted]. [redacted] and [redacted] were also modified for the MitraClip NT Device. The grasping performance was shown to be non-inferior to the former versions in the studies described later in Section "2.(3).2).A.(b) Performance study."

The clips were implanted by thoracotomy. The CDS was inserted through the SGC that had been inserted into the left atrium of each pig. Then, 1 clip was implanted in the mitral valve under radiographic or echocardiographic guidance. During this procedure, the clip was examined for the maneuverability (easiness of direction adjustment, leaflet grasping, operation of the clip arm and gripper, arm inversion of the clip, deployment [release], and removal of the lock line and gripper line) and visibility under radiographic or echocardiographic guidance. At 4, 12, 17, 24, 29, and 52 weeks after clip implantation, the movement of the entire clip and the function of the mitral valve were assessed. In addition, measurement of atrial pressure and ventricular pressure, as well as necropsy, was performed. The removed clips were subjected to histopathological assessment and analysis with a scanning electron microscope (SEM). According to the assessment of the maneuverability (leaflet grasping), "the clip functioned with mild or moderate difficulty" in 1 of 21 animals. This was because the MitraClip NT Device was inserted into the left atrium by thoracotomy, followed by suture of the insertion site, which is not the intended implantation method for the product. In all of other tests, the clip "functioned as intended." The visibility of the MitraClip NT System was satisfactory during all procedures.

There was no death of any animal implanted with the MitraClip NT Device. No noteworthy thrombus, thromboembolus, or infarction was observed in the heart, liver, spleen, kidneys, brain or other organs at any time point. One animal was not examined because the samples of the isolated organs from this animal could not be identified.

Histopathology revealed the tissue covering over time the clip surface and the space between the gripper and the arm, with a hard tissue bridge in the maturation process at the edges of the mitral anterior and posterior leaflets. SEM analysis clearly showed endothelial cells covering the clip at 12 weeks and mature endothelial cells densely covering the clip after 24 weeks.

Two animals had active infective endocarditis as confirmed based on clinical signs, with the presence of bacteria in the mitral valve samples. Histopathology of the mitral valve samples from 4 asymptomatic animals also revealed the presence of bacteria, suggesting infective endocarditis. The mitral valve samples of 3 asymptomatic animals showed localized inflammatory reaction accompanied by polymorphonuclear leukocyte infiltration. Below are 3 possible causes of these events.

Cause 1: The MitraClip NT Device cannot be implanted in pigs using the same procedures as humans. The test device was implanted in pigs by thoracotomy, which is not required in humans. The researchers attempted to maintain the sterile environment and complete the procedures as shortly as possible. It was, however, impossible to create a laboratory environment equivalent to the surgical room for humans. It took 2 to 4 hours on average to complete the procedures. The incidence of postoperative infection is known to be proportional to the duration of operation. In addition, the clips were handled without the protective cover before they were inserted into the animal body, which must not occur in clinical practice.

Cause 2: The MitraClip NT Device was manufactured not in a controlled sterile environment but a minimum clean environment that was feasible at that time. Sterility parameters were not clearly defined.

Cause 3: Postoperative conditions and animal husbandry conditions increase the risk of postoperative infection via blood. Such risk in animals and humans cannot be compared because it is impossible to simply extrapolate those conditions to humans.

The above events were considered as potential risks, although they were not findings obtained in clinical practice. To mitigate these potential risks, measures were taken. The sterile environment conditions, procedures, and sterilization conditions in the manufacturing process will be established by the time when the MitraClip NT System is first used in clinical practice. A precaution was added to the instructions for use to ensure that the protective cover of the clip is not removed until immediately before the use of the clip. No infection has been reported for the MitraClip NT System used in clinical practice.

ii Acute delivery performance and safety of MitraClip NT Device

The study was conducted to evaluate the acute delivery performance and safety of the MitraClip NT Device. The CDS (comparable in [redacted]), to which a clip with [redacted] modified in the development phase was attached, was inserted through the SGC that had been used to introduce the CDS into the left atrium via femoral vein in pigs (n = 4). Then, 1 clip was implanted in the mitral valve under radiographic or echocardiographic guidance. The performance (pushability, trackability, reactivity, and removal) of the MitraClip NT System was evaluated during the preparation and implantation procedures. Then, the test samples were subjected to necropsy and histopathology. One

animal that died from transseptal puncture during preparation and ventricular fibrillation after insertion of the guide wire was excluded from evaluation. Another animal was excluded from evaluation because of a protocol deviation. Table 9 shows the results of the performance tests (pushability, trackability, reactivity, and removal) during the preparation and implantation procedures. The MitraClip NT System was easily visible under radiographic or echocardiographic guidance. No noteworthy abnormality was observed in the assessment of isolated organs including heart, liver, spleen, kidneys, brain, and great blood vessels, or histopathology.

Table 9. Performance evaluation of MitraClip NT System

Animal No.	Result
1	In the test for the capability of grasping the leaflets at the appropriate position and removing the gripper line, the clip "functioned with mild or moderate acceptable difficulty." In all of other tests, the clip "functioned as intended."
2	The steerable guide catheter and the steerable sleeve of the clip delivery system before and after exchange "functioned with mild or moderate acceptable difficulty." The delivery catheter before exchange "functioned with unacceptable difficulty." In all of other tests, the clip "functioned as intended."
3	In all of the tests, the clip "functioned as intended."
4	In the test for clip release, the clip "functioned with mild or moderate acceptable difficulty." In the test for removal of the gripper line, the clip "functioned with unacceptable difficulty." In all of other tests, the clip "functioned as intended."

The pigs used as a test animal had a small left atrium, which interfered with the manipulation of the MitraClip NT System. This may explain those difficulties in manipulation. They are, therefore, very unlikely to occur in humans. Nevertheless, based on the above test results, an improvement was made so that [redacted], and a modification in [redacted]. In addition, risk mitigation measures, such as training of surgeons and modifying the procedures for checking the precautions in the instructions for use, were taken.

iii Safety of repeated grasping

The study was conducted in 3 pigs using the clip with [redacted] modified in the development phase (comparable in [redacted]) to verify that [redacted] repetitions of grasping the mitral leaflets would not damage the mitral valve or tendinous cords. The test animals underwent thoracotomy. The clip was delivered to the mitral valve using the CDS through the SGC for grasping the leaflets. The mitral valve was assessed for its function for at least [redacted]. Then, the clip was released from the mitral valve, and the CDS was retrieved into the left atrium. The mitral valve was assessed for its function after the removal of the clip. After this procedure was repeated [redacted] times, necropsy of organs (e.g., heart, liver, spleen, kidneys, and brain) was performed. The mitral valve was assessed histopathologically.

The performance tests of the MitraClip NT System revealed that the clip was easily inserted into the left atrium of the pigs. In the tests for the following 5 functions during the manipulation of the clip to grasp the leaflets, the MitraClip NT System "functioned as intended": 1) Easiness of direction adjustment, 2) leaflet grasp, 3) operation of the clip arm and gripper, 4) inversion of the clip arm, and 5) release. In the test for 6) visibility under radiographic or echocardiographic guidance, the MitraClip NT System was "clearly visible."

No noteworthy abnormality was observed in the isolated organs.

Histopathology of the mitral valve from 1 of 3 animals showed the extravasation of red blood cells and acute rupture inside the leaflet tissue at a site not grasped with the clip. No animal had a significant injury to the mitral valve. The extravasation of red blood cells appeared to have been caused by a contact between the contact portion of the gripper of the MitraClip device and the leaflets. Findings observed in other organs were mild localized infiltration of mononuclear cells in the liver of 1 animal, and mild localized infiltration of mononuclear cells in the kidneys and moderate bronchopneumonia in 1 animal. These findings were accidental and not related to the procedures.

2.(3).2).A.(b) Performance study

The study was conducted using a heart pulsation model with a pig heart to compare the clip grasping performance before and after the modification of [redacted]. The test sample was the MitraClip NT Device. The control sample was the clip (CDS02) [redacted]. The test and control samples were manipulated to simulate the clinical use. The leaflet grasping procedure (lowering the gripper with the clip arm held at 120°) was repeated [redacted] times. The number of repetitions required to achieve a secure grasp was determined. All of the test samples of the modified version of the clip required 1 try to achieve a secure grasp of the leaflets, showing its improved grasping performance compared with the former version.

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

PMDA reviewed the data on the design verification, animal, and performance studies of the MitraClip NT System 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 MitraClip NT System meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter, referred to as "the Essential Principles") (Public Notice No. 122 of Ministry of Health, Labour and Welfare of 2005).

3.B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with the conformity of the MitraClip NT System to the Essential Principles.

4. Risk Management

4.A Summary of the data submitted

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

4.B Outline of the review conducted by PMDA

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

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on the in-process tests and sterilization methods for the MitraClip NT System.

5.B Outline of the review conducted by PMDA

PMDA reviewed the data on the manufacturing process for the MitraClip NT System 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 (the EVEREST II study [the E II study]) and a Japanese clinical study (Study AVJ-514), both of which evaluated the efficacy and safety of the MitraClip NT System. The E II study consisted of multiple clinical studies. The data submitted also included the results of 12-month follow-up of a randomized controlled trial (RCT) that compared the MitraClip NT System and surgery in non-high-surgical-risk patients (the EVEREST II RCT study [the E II RCT study]), the results of 12-month follow-up of a single-arm foreign clinical study in high-surgical-risk patients with severe MR (EVEREST II High Risk Registry [the E II HRR study]), the results of 24-month follow-up in the first 273 subjects who received single-arm continuous evaluation (EVEREST II REALISM Continued Access Study Risk Cohort, [the Realism HR study]), and the results of an integrated data analysis combining the results in 78 subjects in the E II HRR study and the first 273 subjects in the Realism HR study (Integrated High Risk Cohort) (Table 10).

Table 10. Summary of the clinical data submitted as attached documents

Attached documents					
Study	Study design	Study population	Study device	Control	Location
E II RCT study	Prospective, multicenter, randomized, controlled	MR severity of 3+/4+ Non-high surgical-risk patients	N = 184	Surgery N = 95	US/ Canada
E II HRR study	Prospective, multicenter, single-arm	MR severity of 3+/4+ High-surgical-risk patients	N = 78	-	US/ Canada
Realism HR study	Prospective, multicenter, single-arm N = first 273	MR severity of 3+/4+ High-surgical-risk patients	N = 273	-	US
Integrated High Risk Cohort	Integrated data analysis combining the results from 78 subjects in E II HRR Study and the first 273 subjects in Realism HR Study	MR severity of 3+/4+ High-surgical-risk patients	N = 351	-	US/ Canada
Study AVJ-514	Prospective, multicenter, single-arm	MR severity of 3+/4+ High-surgical-risk patients	N = 30		Japan

Note) In these clinical studies, the previous models of CDS (Realism HR Study, CDS01 and CDS02; Study AVJ-514, CDS02; and other studies, CDS01) were used.

The applicant also submitted the following reference data: the results of 5-year follow-up of "the E II RCT study," the results of 5-year follow-up of "the E II HRR study," "Realism HR Study Periodic Report" (study results as of the data lock date of [redacted][1]), the results of 12-month follow-up of "the EVEREST II Roll-In study," the results of 24-month follow-up of "the Realism Non-HR study" in non-high-surgical-risk patients, "Realism Non-HR Study Periodic Report" (study results as of the data lock date of [redacted]), "Study AVJ-514 Interim Report," and "Integrated High Risk Cohort Periodic Report" (study results as of the data lock date of [redacted]).

Position of each clinical study

After the completion of subject enrollment in the E II RCT study and the E II HRR study, an extension study of the MitraClip NT System (the Realism study) was conducted. The Realism study consisted of 2 groups, non-high-surgical-risk subjects (the Realism Non-HR study) and high-surgical-risk subjects (the Realism HR study). The Realism HR study used the same inclusion and exclusion criteria as those of the E II HRR study, except for the following exclusion criterion specified for the Realism HR study: "patients who are likely to die within 1 year." The study protocol, including primary endpoints and follow-up schedule, did not substantially differ between these studies. Because one of the objectives of the Realism study was to collect additional efficacy and safety data to support the Premarket Approval Application in the US, the protocol of the Realism study defined the evaluation of data from the Integrated High Risk Cohort. A data set from a total of 351 subjects (Integrated High Risk Cohort), combining 78 subjects from the E II HRR study and 273 subjects who completed 12-month follow-up as of [redacted] (the maximum sample size available for the review at the Food and Drug Administration [FDA] Advisory Committee Meeting[2] the on March 20, 2013), was used to evaluate the efficacy and safety of the MitraClip NT System. On the basis of this data set, the MitraClip NT System was approved in the US (Figure 5).

[1] Subject enrollment was continued after the first 273 were enrolled in the study until the investigational device was approved in the US. The data from a total of 628 subjects were submitted.

[2] https://www.fda.gov/AdvisoryCommittees/

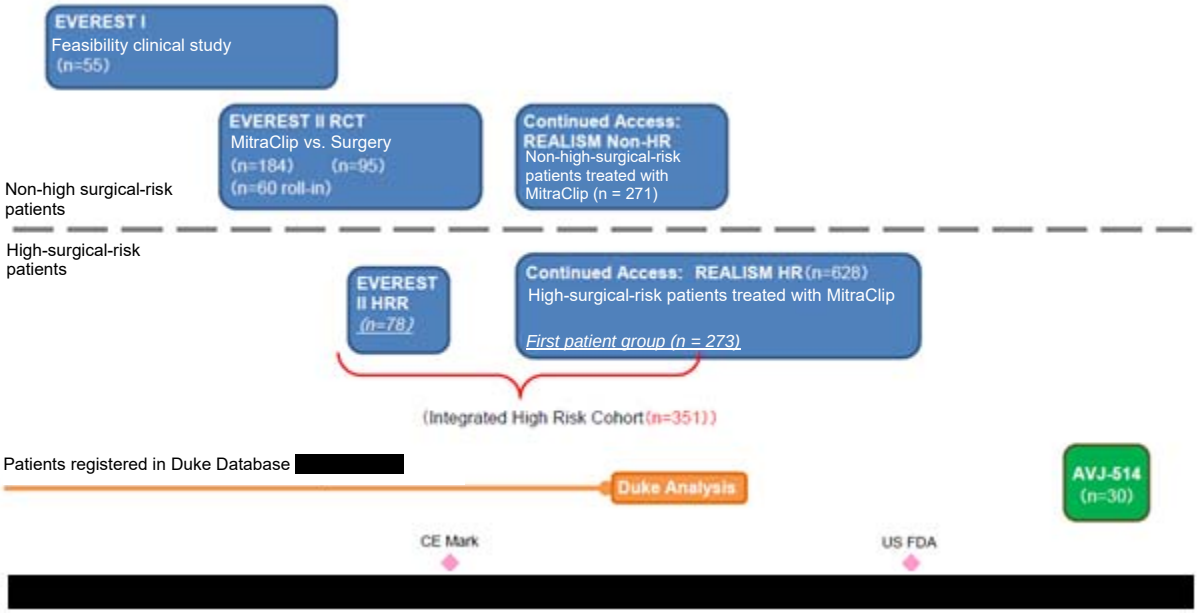


Figure 5. Clinical studies of MitraClip

6.A.(1) E II RCT Study (study period, [redacted] to [redacted])

The E II RCT study was a prospective, multicenter, randomized, controlled study conducted in non-high-surgical-risk patients with severe[3] MR to evaluate the efficacy and safety of the MitraClip NT System versus surgery (Table 11).

[3] The severity of MR was assessed by the Echocardiography Core Laboratory according to the Recommendations for Evaluation of the Severity of Native Valvular Regurgitation with Two-dimensional and Doppler Echocardiography, the guideline issued by American Society of Echocardiography in 2003. The severity is classified into mild (1+), moderate (2+), moderate to severe (3+), or severe (4+).

Table 11. Design of the E II RCT study

Key inclusion criteria	This study enrolled patients aged ≥18 years who met the following criteria: • Patients who have symptomatic and chronic, moderate to severe (3+) or severe (4+) MR, AND who are symptomatic with LVEF >25% and LVIDs ≤55 mm, or asymptomatic with any of the following conditions: - LVEF ≥25% and ≤60%, - LVIDs ≥40 mm, - new onset of atrial fibrillation, or - pulmonary arterial systolic pressure >50 mmHg at rest or >60 mmHg with exercise • Patients who are eligible for mitral valvuloplasty or mitral valve replacement with a heart-lung machine. • Patients with the primary regurgitant jet originating from the A2 and P2 scallops. If a secondary jet is present, it must be considered clinically insignificant.
Key exclusion criteria	• Patients with severe left ventricular dysfunction (LVEF ≤25% and/or LVIDs >55 mm). • Patients with mitral valve orifice area <4.0 cm^2. • If leaflet flail present: - Flail width ≥15 mm - Flail gap ≥10 mm • If leaflet tethering is present: - Mitral valve coaptation depth >11 mm - Length of leaflet coaptation surface <2 mm • Patient with severe calcification in the mitral valve ring. • Patients with leaflet anatomy which may preclude implantation of MitraClip NT Device, proper positioning of MitraClip NT Device on the leaflets, or sufficient reduction in MR. This may include: - Calcification in the grasping area in the A2 and/or P2 scallops - Severe cleft in the A2 or P2 scallop - At least 2 anatomical structural features close to the limits defined in the exclusion criteria - Bileaflet flail or bileaflet prolapse - Lack of both primary and secondary chordal support • Patients with hemodynamic instability defined as having a systolic blood pressure of <90 mmHg without afterload reduction, having cardiogenic shock, or requiring treatment with a cardiotonic agent or intra-aortic balloon pump (IABP).
Primary endpoints	Primary efficacy endpoints To verify the non-inferiority of MitraClip NT System to surgery (non-inferiority margin of 31%) in the PP population, "death, mitral valve surgery (MitraClip group) or re-operation for valvar dysfunction (surgical control group), and freedom from MR >2+ (moderate to severe [3+] or severe [4+]) (clinical success) at Month 12" were selected as primary efficacy endpoints. Primary safety endpoint To demonstrate the superiority of MitraClip NT System to surgery (margin of 6%) in the PP population, "the incidence of the major adverse events* through 30 days" was selected. * The major adverse events were defined as the composite of the following endpoint events: Death, myocardial infarction, re-operation for failed surgical repair or replacement, non-elective cardiovascular surgery for adverse events, stroke, renal failure, deep wound infection, ventilation >48 hours, gastrointestinal complication requiring surgery, new onset of permanent atrial fibrillation, sepsis, and transfusion of ≥2 units of blood

Note) LVEF = Left Ventricular Ejection Fraction, LVIDs = Left Ventricular Internal Dimension – systolic (Hereinafter, the same applies unless otherwise noted.)

A total of 279 patients were enrolled in this clinical study, and 184 subjects randomized to the MitraClip group and 95 subjects randomized to the surgical control group were included in the intent-to-treat (ITT) population. Of them, 21 subjects (6 in the MitraClip group, 15 in the surgical control group) did not receive the assigned treatment (randomized not treated [RNT] population). Except for these subjects, 178 subjects in the MitraClip group and 80 subjects in the surgical control group received their respective assigned treatments. The Per Protocol (PP) population included 137

subjects in the MitraClip group who underwent the MitraClip NT procedure and achieved acute procedural success[4] and 80 subjects in the surgical control group (Figure 6).

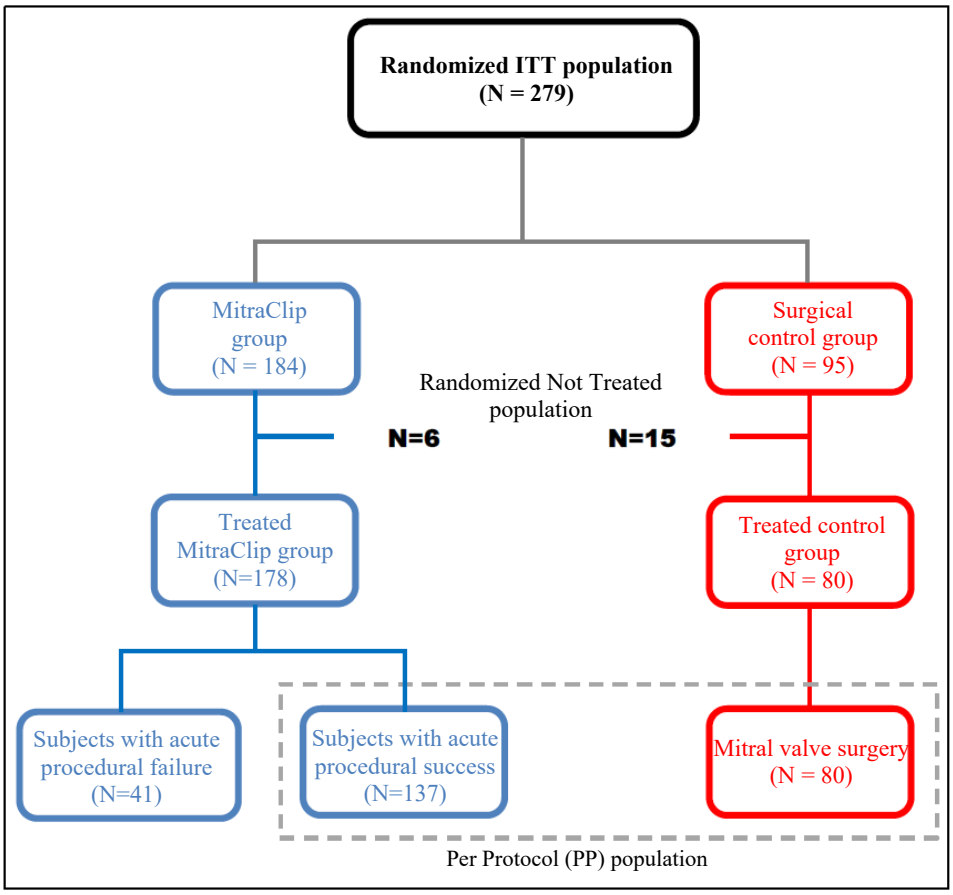


Figure 6. Flow chart of subject composition

Patient characteristics of the MitraClip group and the surgical control group were compared in the PP population, which is the primary analysis population for efficacy and safety evaluation. A significant between-group difference was observed in the proportion of subjects with congestive cardiac failure (92.0% [126 of 137 subjects] in the MitraClip group, 80.0% [64 of 80 subjects] in the control group). The other characteristics did not significantly differ between the groups.

Of 178 subjects who underwent the MitraClip NT procedure, 158 (88.8%) received the MitraClip NT Device and 137 (77%) achieved acute procedural success. Table 12 shows the breakdown of 20 subjects (11.2%) in the MitraClip group who did not receive the MitraClip NT Device.

Table 12. Breakdown of subjects receiving no MitraClip NT Device

Difficulty in transseptal puncture/complications due to transseptal puncture	n = 5
Difficulty in leaflet grasping	n = 6
Insufficient MR reduction	n = 8
Takotsubo cardiomyopathy during the procedure and secondary MR jet that met the exclusion criterion during the second implantation procedure	n = 1

[4] Successful implantation of MitraClip NT Device with MR severity ≤2+ at discharge

6.A.(1).1) Results of primary endpoints

"The incidence of the major adverse events at 30 days in the PP population," the primary safety endpoint, was 9.6% (13 of 136 subjects) in the MitraClip group and 57.0% (45 of 79 subjects) in the surgical control group. The results demonstrated the superiority of the MitraClip NT System to surgery (Table 13). Table 14 shows the incidence of major adverse events.

Table 13. Analysis results for primary safety endpoint (incidence of major adverse events at 30 days)

Incidence of major adverse events at 30 days	MitraClip (N = 137)	Surgical control (N = 80)	Difference between MitraClip and control (%) (two-sided 95% CI)[a]	*P*-value[b]	Test result
Complete Case[c] % (n/N)	9.6% (13/136)	57.0% (45/79)	-47.4% (-60.4%, -34.4%)	< 0.0001	Achieved[d]

[a] The confidence interval (CI) for difference in 2 independent binomial proportion estimates subjected to correction for continuity was calculated by the asymptotic method.

[b] *P*-value of hypothesis test: H_0, $\pi_{MitraClip} + 0.06 \geq \pi_{control}$; H_A, $\pi_{MitraClip} + 0.06 < \pi_{control}$. The *P*-value was calculated by Farrington-Manning's maximum-likelihood method. Whether the endpoint was achieved was concluded based on the *P*-value.

[c] One subject in the MitraClip group and 1 subject in the surgical control group did not have follow-up examination at and after 25 days post-procedure and therefore were not included in the Complete Case analysis.

[d] The significance of the *P*-value in the PP population was based on the significance level of 0.0246 because an interim analysis was performed.

Table 14. E II RCT study: List of major adverse events at 30 days (PP population, N = 217) (Complete Case[a])

Event	MitraClip (N = 137)		Surgical control (N = 80)		Difference between MitraClip and control % (two-sided 95% CI)[b]
	Percentage of subjects % (n/N)	No. of events	Percentage of subjects % (n/N)	No. of events	
Death	0.0% (0/136)	0	2.5% (2/79)	2	-2.5% (-7.0%, 1.9%)
Myocardial infarction	0.0% (0/136)	0	0.0% (0/79)	0	0.0% NA
Re-operation for failed surgical repair or replacement	0.0% (0/136)	0	1.3% (1/79)	1	-1.3% (-4.7%, 2.2%)
Non-elective cardiovascular surgery for adverse events	0.0% (0/136)	0	5.1% (4/79)	5	-5.1% (-10.9%, 0.8%)
Stroke	0.0% (0/136)	0	2.5% (2/79)	2	-2.5% (-7.0%, 1.9%)
Renal failure	0.0% (0/136)	0	0.0% (0/79)	0	0.0% NA
Deep wound infection	0.0% (0/136)	0	0.0% (0/79)	0	0.0% NA
Ventilation >48 hours	0.0% (0/136)	0	5.1% (4/79)	5	-5.1% (-10.9%, 0.8%)
Gastrointestinal complication requiring surgery	0.7% (1/136)	1	0.0% (0/79)	0	0.7% (-1.7%, 3.2%)
New onset of permanent atrial fibrillation	0.0% (0/136)	0	0.0% (0/79)	0	0.0% NA
Sepsis	0.0% (0/136)	0	0.0% (0/79)	0	0.0% NA
Transfusion ≥2 units	8.8% (12/136)	13	53.2% (42/79)	49	-44.3% (-57.3%, -31.3%)
Overall[c]	**9.6% (13/136)**	**14**	**57.0% (45/79)**	**64**	**-47.4% (-60.4%, -34.4%)**
Overall (excluding transfusion ≥2 units)	**0.7% (1/136)**	**-**	**11.4% (9/79)**	**-**	**-10.7% (-18.9%, -2.5%)**

[a] One subject in the MitraClip group and 1 subject in the surgical control group were not included in the Complete Case analysis.

[b] The CI for difference in 2 independent binomial proportion estimates subjected to correction for continuity was calculated by the asymptotic method.

[c] The total number of subjects may not equal the sum of subjects in each row since a subject may experience multiple events.

Table 15 shows the analysis of "the clinical success at 12 months in the PP population," the primary efficacy endpoint of the study. The protocol-defined criteria was achieved. Table 16 shows the reasons for clinical failure.

Table 15. Analysis results for primary efficacy endpoint (clinical success rate at 12 months) (N = 217)

Clinical success rate at 12 months	MitraClip (N = 137)	Surgical control (N = 80)	MitraClip versus control (lower limit of 95% CI)[a]	*P*-value[b]	Test result
Complete Case[c] % (n/N)	72.4% (97/134)	87.8% (65/74)	-15.4% (-25.4%)	0.0012	Achieved[d]

[a] The CI for difference in 2 independent binomial proportion estimates subjected to correction for continuity was calculated by the asymptotic method.

[b] *P*-value of efficacy hypothesis test: H_0, $p_{MitraClip} \leq p_{control} - 0.31$; H_A, $p_{MitraClip} > p_{control} - 0.31$. Whether the endpoint was achieved was concluded based on the *P*-value.

[c] Of the 3 subjects in the MitraClip group, 1 subject who dropped out from the study and 2 subjects with missing data at 12 months were not included in the Complete Case analysis. Of the 6 subjects in the control group, 4 subjects who withdrew consent or lost to follow-up and 2 subjects with missing data at 12 months were not included in the Complete Case analysis.

[d] The significance of the *P*-value was based on the significance level of 0.05.

Table 16. Reasons for clinical failure at 12 months (PP population, N = 217)[a]

Reason	MitraClip % (n/N)	Surgical control % (n/N)	Difference between MitraClip and surgical control (two-sided 95% CI[b])
Death	4.5% (6/134)	6.8% (5/74)	-2.3% (-10.0%, 5.5%)
Mitral valve surgery (MitraClip group) or re-operation (surgical control group)	6.7% (9/134)	2.7% (2/74)	4.0% (-2.7%, 10.7%)
MR severity >2+	16.4% (22/134)	2.7% (2/74)	13.7% (5.4%, 22.0%)
Total	27.6% (37/134)	12.2% (9/74)	15.4% (3.8%, 27.1%)

[a] Three subjects in the MitraClip group and 6 subjects in the surgical control group were not included in the Complete Case analysis.

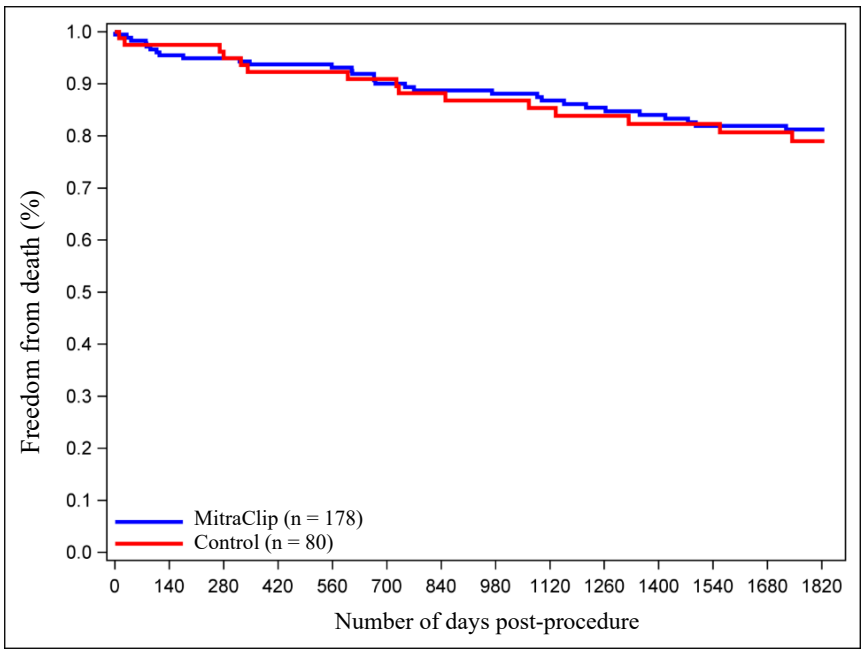
[b] The CI for difference in 2 independent binomial proportion estimates subjected to correction for continuity was calculated by the asymptotic method.

In general, surgical success is defined as the remaining MR ≤1+ (mild or less). An additional analysis was performed using a new definition for clinical success "an MR severity of ≤1+." The analysis showed that the difference in the PP population was −23.8% (95% LCB = −37.7%, *P* = 0.1692). When the clinical success was defined as "an MR severity of ≤1+," the study failed to demonstrate the non-inferiority of the MitraClip NT System.

6.A.(1).2) Long-term outcome

6.A.(1).2).(a) Freedom from all-cause death

Freedom from all-cause death at 5-year follow-up was comparable between the MitraClip group (81.2%) and the surgical control group (79.0%) (Figure 7).



Months/years post-procedure	Baseline	12 months	24 months	3 years	4 years	5 years
MitraClip						
Number of high-risk subjects	178	158	143	133	119	58
Number of subjects censored	0	9	18	24	32	90
Number of events	0	11	17	21	27	30
Freedom from event	100%	93.7%	90.0%	87.5%	83.4%	81.2%
95% CI	-	[88.8%, 96.5%]	[84.2%, 93.8%]	[81.1%, 91.8%]	[76.2%, 88.5%]	[70.1%, 88.5%]
Control						
Number of high-risk subjects	80	70	65	57	52	24
Number of subjects censored	0	4	7	12	15	41
Number of events	0	6	8	11	13	15
Freedom from event	100%	92.3%	89.6%	85.3%	82.3%	79.0%
95% CI	-	[83.5%, 96.5%]	[79.9%, 94.7%]	[74.3%, 91.9%]	[70.5%, 89.8%]	[59.9%, 89.7%]

Note) After 5 years (1,825 days), 2 subjects died (at 1,834 and 1,839 days). These subjects were excluded from analysis.

Figure 7. Kaplan-Meier estimate of freedom from all-cause death through 5 years (ITT population) (N = 258)

6.A.(1).2).(b) MR severity

Subjects in the surgical control group had more reduction in MR throughout the entire follow-up period compared with subjects in the MitraClip group. Approximately 81% to 85% of the subjects in the MitraClip group and 94% to 100% of subjects in the surgical control group achieved MR ≤2+ through 5 years. Approximately 36% to 53% of the subjects in the MitraClip group and 77% to 93% of subjects in the surgical control group achieved MR ≤1+ (Table 17).

Table 17. MR Severity at baseline and follow-up
MitraClip group (Treated: N = 178)

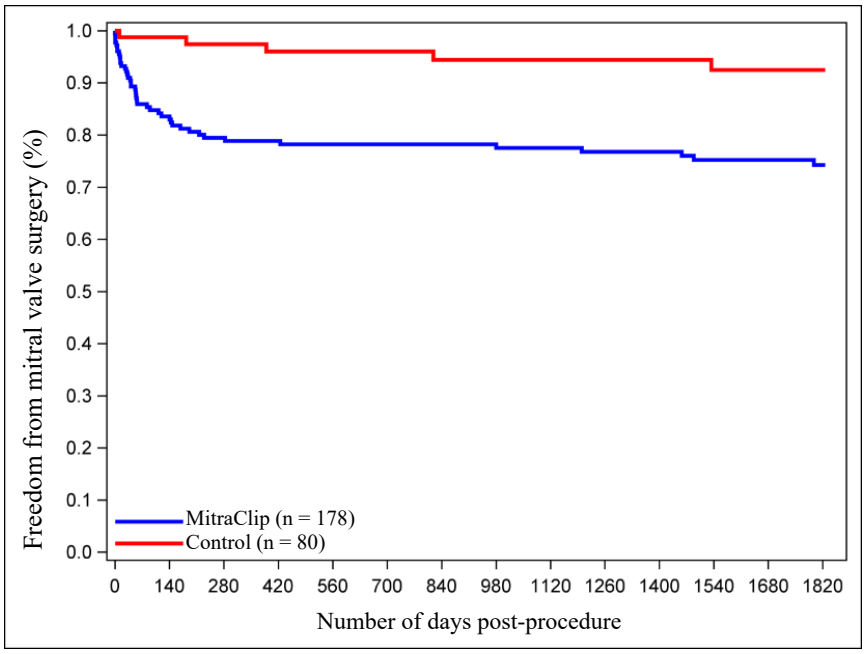
Severity	Follow-up point	N	Baseline	Follow-up	Difference (follow-up vs. baseline)
MR ≤2+ (% of subjects)	Discharge	173	4.0%	83.8%	79.8%
	12 months	149	4.0%	81.2%	77.2%
	24 months	127	3.9%	85.0%	81.1%
	3 years	122	3.3%	84.4%	81.1%
	4 years	105	2.9%	81.0%	78.1%
	5 years	106	1.9%	82.1%	80.2%
MR ≤1+ (% of subjects)	Discharge	173	0.0%	52.6%	52.6%
	12 months	149	0.0%	43.0%	43.0%
	24 months	127	0.0%	36.2%	36.2%
	3 years	122	0.0%	39.3%	39.3%
	4 years	105	0.0%	42.9%	42.9%
	5 years	106	0.0%	50.0%	50.0%

Surgical control group (Treated: N = 80)

Severity	Follow-up point	N	Baseline	Follow-up	Difference (follow-up vs. baseline)
MR ≤2+ (% of subjects)	Discharge	76	6.6%	100%	93.4%
	12 months	66	7.6%	98.5%	90.9%
	24 months	57	10.5%	96.5%	86.0%
	3 years	50	8.0%	96.0%	88.0%
	4 years	49	8.2%	93.9%	85.7%
	5 years	41	9.8%	97.6%	87.8%
MR ≤1+ (% of subjects)	Discharge	76	0.0%	84.2%	84.2%
	12 months	66	0.0%	77.3%	77.3%
	24 months	57	0.0%	84.2%	84.2%
	3 years	50	0.0%	86.0%	86.0%
	4 years	49	0.0%	85.7%	85.7%
	5 years	41	0.0%	92.7%	92.7%

6.A.(1).2).(c) Freedom from mitral valve surgery

The Kaplan-Meier estimate of freedom from mitral valve surgery at 5 years was 74.3% in the MitraClip group and the 92.5% in the surgical control group (Figure 8).



Months/years post-procedure	Baseline	12 months	24 months	3 years	4 years	5 years
MitraClip						
Number of high-risk subjects	178	128	117	109	98	45
Number of subjects censored	0	13	23	30	39	90
Number of events	1	37	38	39	41	43
Freedom from event	99.4%	78.9%	78.2%	77.6%	76.0%	74.3%
95% CI	[96.1%, 99.9%]	[71.7%, 84.4%]	[70.7%, 84.0%]	[69.7%, 83.6%]	[67.7%, 82.5%]	[61.3%, 83.5%]
Control						
Number of high-risk subjects	80	69	63	54	49	21
Number of subjects censored	0	9	14	22	27	54
Number of events	0	2	3	4	4	5
Freedom from event	100%	97.4%	96.0%	94.4%	94.4%	92.5%
95% CI	-	[89.5%, 99.4%]	[87.2%, 98.8%]	[84.2%, 98.1%]	[83.4%, 98.2%]	[70.4%, 98.3%]

Note) The Kaplan-Meier estimation through 5 years (1,825 days) included the first surgery at 55 days in 1 subject in the MitraClip group but excluded the additional surgery at 1,015 days in this subject.

Figure 8. Kaplan-Meier curves of freedom from mitral valve surgery in the MitraClip group and freedom from additional surgery in the control group through 5 years (ITT population) (N = 258)

6.A.(2) E II HRR study and Realism HR study

6.A.(2).1) E II HRR study (study period, [redacted] to [redacted])

The E II HRR study was a prospective, multicenter, single-arm study conducted in patients with symptomatic severe MR (MR severity 3+/4+) who were deemed at high risk for surgery by a surgeon based on a Society of Thoracic Surgeons (STS) risk score for mitral valve replacement[5] ≥12% or the presence of a risk factor(s) to evaluate the efficacy and safety of the MitraClip NT System. Table 18 shows the primary study design.

[5] Predicted procedural mortality calculated according to the formula developed by the STS

Table 18. Design of the E II HRR study

Key inclusion criteria	This study enrolled patients aged ≥18 years who met the following inclusion criteria: • Patients considered at high risk for surgery by a surgeon based on an STS risk score for mitral valve replacement ≥12% or the presence of pre-defined risk factor(s).* * The risk factors include the following: Porcelain aorta or mobile ascending aorta atheroma, post-radiation mediastinum, past history of mediastinitis, functional MR with LVEF <40%, >75 years of age with LVEF <40%, re-operation with patent grafts, ≥2 prior cardiovascular surgeries, hepatic cirrhosis, ≥3 surgical risk factors (creatinine >2.5 mg/dL, prior cardiovascular surgery, >75 years of age, LVEF <35%). • Patients with symptomatic and chronic moderate to severe (3+/4+) MR whose symptoms is likely to be mitigated by MR reduction, according to investigator's opinion. • Patients with MR from the same area with the primary regurgitant jet originating from malcoaptation of the A2 and P2 scallops of the mitral valve.
Key exclusion criteria	• Patients with severe left ventricular hypofunction (LVEF ≤20% and/or LVIDs >60 mm). • Patients with mitral valve area <4.0 cm^2. • Patient with any of the following anatomical findings: ➢ If leaflet flail is present: • Flail width ≥15 mm • Flail gap ≥10 mm ➢ If leaflet tethering is present: • Coaptation length <2 mm ➢ Patients with leaflet anatomy which may preclude implantation of MitraClip NT Device, proper positioning of MitraClip NT Device on the leaflets, or sufficient reduction in MR • Calcification in the grasping area in the A2 and/or P2 scallops • Severe cleft in the A2 or P2 scallop • At least 2 anatomical structural features close to the limits defined in the exclusion criteria • Bileaflet flail or bileaflet prolapse • Lack of both primary and secondary chordal support • Patients with hemodynamic instability (defined as having systolic blood pressure of <90 mmHg without afterload reduction or cardiogenic shock, or requiring treatment with a cardiotonic agent or IABP).
Primary endpoints	To verify that MitraClip NT System is associated with a lower procedural mortality than predicted procedural mortality risk in the ITT population, "the long-term mortality at 30 days post-procedure or discharge" was selected as the primary efficacy endpoint.

The predicted procedural mortality risk was calculated using the STS Calculator. The calculated STS score was used as a predicted risk of procedural mortality when it was ≥12%, while the predicted procedural mortality risk was perioperatively estimated by a surgeon when the calculated STS score was <12%.

6.A.(2).1).(a) Results of primary endpoints

"The long-term mortality within 30 days of the procedure or discharge post-procedure, whichever is longer," the primary efficacy endpoint, was 7.7% (6 of 78 subjects), showing a significant difference from the predicted procedural mortality risk (18.2%) estimated as above (P = 0.006). On the other hand, the predicted procedural mortality risk (14.2%) determined more conservatively based on the STS scores calculated in all subjects using the STS Calculator, as requested by the FDA, showed no significant difference from the procedural mortality (P = 0.057).

Of 78 subjects who underwent the MitraClip NT procedure, 56 (71.8%) achieved acute procedural success.

6.A.(2).1).(b) Comparison with retrospectively collected data

To compare freedom from death at 30 days and 12 months in the MitraClip group with that in the medical therapy group, data were collected retrospectively from subjects as control. The control subjects had been screened for the study to meet the inclusion criteria regarding MR severity and high risk for surgery, but were not enrolled in the study because of, for example, not meeting the anatomical requirements for implantation of the MitraClip NT Device. [redacted]. Consequently, the above subjects were excluded from the analysis, and 36 subjects were enrolled in this control group.

Of 78 subjects who underwent the MitraClip NT procedure in the E II HRR study, 19 died through 12 months. For reference, a comparison at 12 months showed significantly high freedom from death in the MitraClip group (75.6% [59 of 78 subjects]) than the control group (55.6% [20 of 36 subjects]) (*P* = 0.0482).

6.A.(2).2) Realism HR study (study period; [redacted] to [redacted])

The Realism HR study was conducted as an extension study of MitraClip NT System after the completion of subject enrollment in the E II HRR study. A data set from a total of 351 subjects, combining first 273 subjects who completed the 12-month follow-up as of [redacted] (the maximum sample size available for the review at the Advisory Committee Meeting held by the FDA on March 20, 2013) and 78 subjects from the E II HRR study, was used for evaluation (Integrated High Risk Cohort).

Subject enrollment in the Realism HR study continued until the FDA Premarket Approval was granted. A total of 628 subjects were enrolled in the study [for the results, see Section "6.A.(5) Realism HR study," described later].

6.A.(3) Integrated High Risk Cohort

An analysis was performed for the data combining the results from 78 subjects in the E II HRR study, which was conducted in symptomatic severe MR subjects who were at high risk for surgery as determined according to the E II study protocol-defined procedure, and from the first 273 subjects in the Realism HR study. The poolability of the protocol-defined baseline characteristics (Table 19) was assessed. The proportion of subjects in each age or comorbidity subgroup did not differ between the 2 groups. The left ventricular ejection fraction (LVEF) and left ventricular internal dimension - systolic (LVIDs) subgroups showed a significant between-group difference. Nevertheless, the baseline data of these factors were considered poolable because both studies enrolled patients with left cardiac function failure, excluding severe patients. Functional MR is associated with a lower LVEF and higher LVIDs than degenerative MR. The Realism HR study included a larger proportion of subjects with functional MR, and therefore its study population had a lower LVEF and higher LVIDs at baseline than the population of the E II HRR study. For this reason, data were stratified by MR type (degenerative MR and functional MR) for analysis [see Section "6.A.(3).5) Assessment of degenerative MR and functional MR," described later].

Table 19. Baseline patient characteristics in the E II HRR study (N = 78) and the Realism HR study (N = 273)

Baseline characteristic % (n/N)	E II HRR Study (N = 78)	Realism HR Study (N = 273)	*P*-value[a]
Age (years), mean ± SD (N)	76.7 ± 9.8 (78)	75.5 ± 10.7 (273)	0.353
Female	37.2% (29/78)	39.6% (108/273)	0.793
BMI (kg/m^2), mean ± SD (N)	26.6 ± 5.0 (78)	26.9 ± 12.9 (273)	0.749
Past history of atrial fibrillation	61.6% (45/73)	70.5% (172/244)	0.155
Diabetes	41.0% (32/78)	39.0% (106/272)	0.793
Myocardial infarction	55.8% (43/77)	49.3% (134/272)	0.366
Chronic obstructive pulmonary disease			0.223
With home oxygen therapy	10.3% (8/78)	11.4% (31/272)	
Without home oxygen therapy	24.4% (19/78)	15.8% (43/272)	
None	65.4% (51/78)	72.8% (198/272)	
Stroke	10.3% (8/78)	13.6% (37/273)	0.565
NYHA class III/IV	89.7% (70/78)	83.5% (228/273)	0.211
Functional MR	59.0% (46/78)	73.3% (200/273)	0.018
Prior cardiovascular operation	59.0% (46/78)	60.1% (164/273)	0.896
LVIDs (cm), mean ± SD (N)	3.9 ± 1.1 (78)	4.5 ± 1.1 (245)	< 0.0001
LVEF (%), mean ± SD (N)	54.4 ± 13.7 (78)	45.2 ± 13.6 (240)	< 0.0001

[a] Non-paired t-test for continuous variables, Fisher's exact test for binary variables, and Bowker method for categorical variables

Note) Having a smaller number of subjects or a smaller denominator than the total sample size of each study represents the presence of missing data.

Of 351 subjects in this cohort, 151 had an STS score ≥12%, and the remaining 200 subjects had an STS score <12%. The latter group of subjects had at least 1 of the protocol-defined risk factors for surgery and were deemed at high risk for mitral valve surgery by a cardiac surgeon (Table 20).

Table 20. Breakdown of surgical risk factors

Protocol-defined surgical risk factor[a]	STS score <12% (N = 200)
Functional MR with LVEF <40%	52.0% (104/200)
Re-operation with patent grafts	49.0% (98/200)
At least 2 prior cardiovascular surgeries	20.5% (41/200)
Age >75 years with LVEF <40%	25.5% (51/200)
At least 3 surgical risk factors[b]	8.0% (16/200)
Hepatic cirrhosis	3.0% (6/200)
Porcelain aorta or mobile ascending aorta atheroma	3.5% (7/200)
Post-radiation mediastinum	4.0% (8/200)

[a] Subjects may be included in more than one category.

[b] Creatinine >2.5 mg/dL, prior cardiovascular surgery, >75 years of age, LVEF <35%

In the Integrated High Risk Cohort, 83.2% (292 of 351) of subjects achieved acute procedural success. The results of other efficacy and safety evaluations are shown below.

6.A.(3).1) Mortality within 30 days of the procedure or discharge post-procedure, whichever is longer

The mortality within 30 days of the MitraClip NT procedure was 4.8% (17 of 351 subjects). This value was significantly lower than the predicted procedural mortality risk (11.3%), which was obtained assuming that the same subjects underwent the surgery (Table 21).

Table 21. Comparison of actual procedural mortality and predicted procedural mortality risk

	(N = 351)
Procedural mortality (actual mortality)	4.8% (17/351)
Upper limit of 95.0% CI[a]	7.6%
Mean predicted procedural mortality risk (based on the calculated STS scores in all subjects)	11.3% ($P < 0.0001$)[b]
95% CI	(10.5%, 12.1%)

[a] The upper limit of the CI is based on the Clopper-Pearson method.
[b] The *P*-values are based on Monte-Carlo simulation.

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

6.A.(3).2).(a) Adverse events adjudicated by the Clinical Events Committee (CEC)

Table 22 shows the incidence of CEC-adjudicated major adverse events reported at 30 days or 12 months (including events reported within 30 days).

Table 22. Incidence of CEC-adjudicated major adverse events at 30 days or 12 months (N = 351)

Major adverse event	(n/N)	
	30 days	12 months
Death	4.8% (17/351)	22.8% (80/351)
Myocardial infarction	1.1% (4/351)	2.3% (8/351)
Re-operation for failed surgical repair or replacement	0.0% (0/351)	0.0% (0/351)
Non-elective cardiovascular surgery for adverse events	0.3% (1/351)	0.3% (1/351)
Stroke	2.6% (9/351)	3.4% (12/351)
Renal failure	1.7% (6/351)	5.4% (19/351)
Deep wound infection	0.0% (0/351)	0.0% (0/351)
Ventilation >48 hours	2.8% (10/351)	5.4% (19/351)
Gastrointestinal complication requiring surgery	0.3% (1/351)	1.4% (5/351)
New onset of permanent atrial fibrillation	0.3% (1/351)	0.3% (1/351)
Sepsis	0.9% (3/351)	4.3% (15/351)
Transfusion ≥2 units	13.4% (47/351)	22.5% (79/351)
Total[a]	**18.8% (66/351)**	**37.6% (132/351)**
Total[a] (excluding transfusion ≥2 units)	**9.1% (32/351)**	**27.9% (98/351)**

[a] The total number of subjects may not equal the sum of subjects in each row since a subject may experience multiple events.

Death was reported in 80 subjects at 12 months (410 days). Of them, 20 subjects experienced adverse events that was adjudicated by the CEC to be procedure- or device-related (the adverse events included those whose relationship with the procedure or device was undeterminable). The device- or procedure-related mortality was 5.7% (20 of 351 subjects).

No adverse event was adjudicated by the CEC as being “Related” to the device. The event in 1 subject was “Probably related” to the device. The events in 6 subjects were “Possibly related” to the device. Deaths suspected to be related to the device occurred in 9 subjects (2.3%), including 1 subject with an event whose relationship with the device was “Undeterminable” and 1 subject with an event that was “Unlikely related” to the device. On the other hand, adverse events in 4 subjects was “Related” to the procedure, the events in 7 subjects were “Probably related” to the procedure, and the events in 2 subjects were “Possibly related” to the procedure.

The most common major adverse event was transfusion ≥2 units. Table 23 shows its detailed information. Many cases of transfusion at 30 days were associated with procedure-related hemorrhage.

From 31 days onwards, transfusion was given to treat anemia in 9 subjects and hemorrhage of digestive tract in 10 subjects.

Table 23. Reasons for transfusion ≥2 units (N = 351), as adjudicated by CEC

Reason	At 30 days	From ≥31 days to 12 months
Hemorrhage at access site during MitraClip NT procedure	19 (40.4%)	1 (3.1%)
Hemorrhage at access site during cardiac operation	2 (4.3%)	2 (6.3%)
Hemorrhage from chest wall/thorax	1 (2.1%)	1 (3.1%)
Anemia	9 (19.1%)	9 (28.1%)
Hemorrhage of digestive tract	7 (14.9%)	10 (31.3%)
Hemorrhage of digestive tract due to a TTE/tracheal tube-caused injury	1 (2.1%)	0 (0.0%)
Pericardial effusion	1 (2.1%)	0 (0.0%)
Pleural effusion	0 (0.0%)	1 (3.1%)
Prophylaxis	3 (6.4%)	3 (9.4%)
Others/unidentified hemorrhage	4 (8.5%)	5 (15.6%)
Total	**47 (100%)**	**32 (100%)**

Table 24 shows a summary of other adverse events. The most common adverse event was major hemorrhagic complications. In this study, major hemorrhagic complications were defined as procedure-related hemorrhage requiring transfusions of ≥2 units and/or surgical intervention. Many of the major hemorrhagic complications reported at 30 days occurred at the access site of the MitraClip NT System (20 of 34 events). One of the possible reason for these complications was the use of a catheter system with a large diameter (24 F).

Table 24. Incidence of CEC-adjudicated other adverse events at 30 days or 12 (N = 351)

Event	% (n/N)	
	30 days	12 months
Major hemorrhagic complications	9.7% (34/351)	11.7% (41/351)
Major vascular complications	3.4% (12/351)	4.0% (14/351)
Non-cerebral thromboembolism	0.3% (1/351)	0.6% (2/351)
Endocarditis	0.0% (0/351)	0.3% (1/351)
Thrombosis	0.0% (0/351)	0.0% (0/351)
Hemolysis	0.0% (0/351)	0.0% (0/351)
Atrial septal defect requiring intervention	1.7% (6/351)	3.1% (11/351)
New onset of permanent atrial fibrillation	2.6% (9/351)	6.8% (24/351)
Heart block/other arrhythmia requiring permanent pacemaker	1.1% (4/351)	2.6% (9/351)

6.A.(3).2).(b) Study site-reported serious adverse events

Table 25 shows a summary of study site-reported serious adverse events. Serious adverse events occurring at the incidence rate of ≥0.2 per patient-year were cardiac events (conduction disorder and cardiac failure congestive), gastrointestinal events (hemorrhage), hematological events (anemia), renal events (renal insufficiency/renal failure), respiratory events (pleural effusion and respiratory failure), vascular events (hemorrhagic complications and hemodynamic instability) at 30 days, and cardiac events (cardiac failure congestive) from >30 days to ≤12 months.

Table 25. Incidence rate of study site-reported serious adverse events

Category of adverse events	Incidence rate At 30 days	Incidence rate From >30 days to ≤12 months	Incidence rate From >12 months to 3 years
Cardiac	2.21 (61)	0.71 (188)	0.39 (80)
Gastrointestinal	0.51 (14)	0.23 (62)	0.09 (19)
Hematological	1.05 (29)	0.13 (35)	0.07 (15)
Musculoskeletal	0.00 (0)	0.01 (3)	0.00 (1)
Nervous	0.29 (8)	0.08 (21)	0.07 (15)
Renal	0.87 (24)	0.13 (35)	0.08 (17)
Respiratory	1.30 (36)	0.30 (80)	0.21 (43)
Vascular	1.45 (40)	0.08 (22)	0.04 (9)
Others	0.80 (22)	0.26 (70)	0.15 (31)

Note) The figures in parentheses in the table represent the number of events.
The incidence rate is the number of events per patient-year. In subjects who were discontinued from the study because of death or dropout, the patient-year is calculated as follows: (Date of discontinuation − Date of procedure)/365.

6.A.(3).3) Echocardiographic endpoints

6.A.(3).3).(a) Changes in MR severity at 12-month follow-up

The severity of MR was assessed by the Echocardiography Core Laboratory (ECL) according to the US echocardiography guidelines. Table 26 shows changes in MR severity at 12 months. The proportion of surviving subjects with an MR severity of ≤2+ was 85.8% (290 of 338 subjects) at discharge, showing improvement from baseline. It was 84.3% (198 of 235 subjects) at 12 months, indicating a sustained MR reduction.

Table 26. MR severity at baseline and follow-up (N = 351)

MR severity	At baseline % (n/N)	At discharge % (n/N)[a]	At 12 months % (n/N)
0: None	0	0	0.9% (2/235)
1+: Mild	0.6% (2/337)	46.4% (157/338)	36.6% (86/235)
1+ to 2+: Mild to moderate	0.9% (3/337)	18.3% (62/338)	20.4% (48/235)
2+: Moderate	12.2% (41/337)	21.0% (71/338)	26.4% (62/235)
3+: Moderate to severe	61.7% (208/337)	10.9% (37/338)	11.9% (28/235)
4+: Severe	24.6% (83/337)	3.3% (11/338)	3.8% (9/235)
Total of subjects not evaluated	14[b]	13	116
Death before assessment	0	2[c]	80
Dropout	0	3	16
No follow-up	0	0	8
No MR data	0	8	12

[a] Only when echocardiographic data at discharge were missing, data at 30 days were used.
[b] The MR severity was assessed as ≥3+ by the study site at the time of enrollment, but it could not be adjudicated by the ECL.
[c] Number of deaths at 30 days

Table 27 shows the analysis results of MR severity at 12-month follow-up based on the MR severity at discharge only in evaluable subjects.

Table 27. Analysis of MR severity at discharge and 12 months[a] (only in evaluable subjects)

MR severity at discharge	MR severity at 12 months				Number of evaluable subjects
	≤1+	2+	3+	4+	
1+	54 (47.0%)	48 (41.7%)	13 (11.3%)	0	115
2+	26 (28.3%)	53 (57.6%)	10 (10.9%)	3 (3.3%)	92
3+	6 (26.0%)	7 (30.4%)	5 (21.7%)	5 (21.7%)	23
4+	0 (0%)	1 (50.0%)	0 (0%)	1 (50.0%)	2
Number of evaluable subjects	86 (37.1%)	109 (47.0%)	28 (12.1%)	9 (3.9%)	232

[a] MR severity was assessed by the ECL in 338 subjects at discharge, 235 subjects at 12 months, and 232 subjects at both discharge and 12 months.

A more conservative analysis of MR severity was performed by including subjects excluded from the above analysis because of death or missing data. Table 28 shows the analysis results assuming that their MR severity was ≥3+.

Table 28. MR reduction at 12 months - results of conservative analysis

Included	**Excluded**	**Subjects with MR severity ≤2+ at 12 months % (n/N)**
Subjects with paired data at baseline and 12 months who completed the study	• Death prior to 12-month follow-up (n = 80) • Surviving subjects with missing data at baseline or 12 months (n = 46)	83.6% (188/225)
Subjects with paired data at baseline and 12 months who completed the study and subject with missing data • MR severity in subjects with missing data was imputed as ≥3+.	• Death prior to 12-month follow-up (n = 80)	69.4% (188/271)
Subjects with paired data at baseline and 12 months who completed the study and subjects who died • MR severity in dead subjects was imputed as ≥3+.	• Surviving subjects with missing data at baseline or 12 months (n = 46)	61.6% (188/305)
All subjects: • MR severity in dead subjects or subjects with missing data was imputed as ≥3+.	None	53.5% (188/351)

6.A.(3).3).(b) Evaluation of cardiac function at 12-month follow-up

Table 29 shows the changes in left ventricular volume and left ventricular dimension assessed by the ECL at baseline and 12-month follow-up. All of the 4 variables of the left ventricular volume and left ventricular dimension showed a significant decrease from baseline at 12-month follow-up, with a reduction of 17.9 mL in Left Ventricular End Diastolic Volume (LVEDV) and 0.2 cm in Left Ventricular Internal Diameter - diastolic (LVIDd).

Table 29. Changes in left ventricular volume and left ventricular dimension[a]

Left ventricular measurement	N	Baseline	12 months	Difference (12-month vs. Baseline)	*P*-value[b]
LVEDV, mL					
Mean ± SD	203	160.5 ± 55.9	142.6 ± 53.1	-17.9 ± 31.8	< 0.0001
LVIDd, cm					
Mean ± SD	221	5.6 ± 0.8	5.4 ± 0.8	-0.2 ± 0.4	< 0.0001
LVESV, mL					
Mean ± SD	202	87.0 ± 46.8	78.9 ± 43.9	-8.1 ± 23.2	< 0.0001
LVIDs, cm					
Mean ± SD	210	4.3 ± 1.1	4.1 ± 1.1	-0.1 ± 0.6	0.0022

[a] Analysis in subjects with data at both time points
[b] Paired t-test
Note) LVEDV = Left Ventricular End Diastolic Volume, LVIDd = Left Ventricular Internal Diameter - diastolic, LVESV = Left Ventricular End Systolic Volume, (hereinafter the same applies unless otherwise noted)

6.A.(3).3).(c) Mitral valve stenosis

In this study, mitral valve stenosis was defined as a mitral valve area of <1.5 cm^2 based on measurements by the ECL. Table 30 shows changes in mitral valve area at 12 months in the Integrated High Risk Cohort (N = 351). One subjects (0.3%) had mitral valve stenosis at 12 months.

Table 30. Mitral valve area (N = 351)[a]

		Baseline	30 days	12 months
Mitral valve area (cm^2)				
Planimetry	Mean ± SD	5.2 ± 1.2	3.1 ± 0.9	2.9 ± 0.8
	(n)	(307)	(234)	(157)
	Median	5.0	2.9	2.9

[a] N represents the number of subjects who underwent the examination at each time point.

6.A.(3).4) Clinical endpoints

6.A.(3).4).(a) Rate of hospitalization for cardiac failure

The rate of hospitalization for cardiac failure 12 months pre-MitraClip procedure and that 12 months post- MitraClip procedure from discharge were compared. For the protocol defined "hospitalization for cardiac failure," patients had to meet all of the following conditions:

- Requiring hospitalization of ≥24 hours for treatment at inpatient facilities or hospital wards including emergency units,
- having clinical signs and/or symptoms of cardiac failure (dyspnea, orthopnea, paroxysmal nocturnal dyspnea, increased fatigue, decreased function, activity intolerance, and new onset or worsening of signs and/or symptoms of volume overload), and
- requiring intravenous infusion (e.g., diuretics and vasoactive drugs) or invasive therapy (e.g., ultrafiltration, intra-aortic balloon pumping, and mechanical support) for the treatment of cardiac failure.

An analysis using a Poisson regression model demonstrated that the rate of hospitalization for cardiac failure from post-discharge through 12 months significantly decreased from that for 12 months pre-procedure (decrease from 0.77 to 0.33 per patient-year) ($P < 0.0001$) (Table 31). The model included subjects who died or were discontinued from the study after discharge, using the duration of the follow-up period for correction.

Table 31. Hospitalization for cardiac failure

	12 months pre-MitraClip procedure	12 months post-MitraClip procedure from discharge	*P*-value
Number of subjects Number of subjects per year	351 351.00	351 292.17	-
Total number of subjects hospitalized Total number of hospitalizations	147 270	58 97	-
Rate of hospitalization per patient-year[a] (two-sided 95% CI)	0.77 (0.68, 0.87)	0.33 (0.27, 0.41)	< 0.0001

[a] The *P*-values and CIs were calculated using the Poisson regression model.

To assess the effects of missing data because of death or study discontinuation after discharge, an analysis was performed using only subjects with 12-month follow-up data after discharge (N = 247). The results of this additional analysis were consistent with the above results (rate of hospitalization, 0.67 at 12 months pre-procedure, 0.24 at 12 months post-discharge). The percentage of subjects on pharmacotherapy for cardiac failure and the types of pharmacotherapy did not significantly differ between before and after the MitraClip NT procedure. Most subjects continued on the same pharmacotherapy after the procedure.

6.A.(3).4).(b) NYHA[6] Functional Class

Table 32 shows the NYHA Classes at baseline and 12-month follow-up. The proportion of evaluable subjects with a NYHA Functional Class ≤II at 12 months was 82.9% (194 of 234 subjects).

Table 32. NYHA Functional Classes at baseline and 12-month follow-up (N = 351)

NYHA	Baseline % (n/N)	12 months % (n/N)
I	2.6% (9/351)	37.6% (88/234)
II	12.5% (44/351)	45.3% (106/234)
III	61.5% (216/351)	15.4% (36/234)
IV	23.4% (82/351)	1.7% (4/234)
Total of subjects evaluated	0	117
Death before assessment	0	80
Dropout	0	16
No follow-up	0	8
No NYHA data	0	13

Table 33 shows the analysis results of the NYHA Functional Class at baseline and 12-month follow-up only in evaluable subjects.

[6] New York Heart Association
The NYHA Functional Class is used to assess the severity of cardiac failure based on the level of physical activity capacity. Severity is classified as asymptomatic (Class I), mild (Class II), moderate to severe (Class III), and refractory (Class IV).

Table 33. Analysis of NYHA Functional Class at baseline and 12 months[a] (evaluable subjects)

Baseline NYHA Functional Class	NYHA Functional Class at 12 months				Number of evaluable subjects
	I	II	III	IV	
I	4 (66.6%)	2 (33.3%)	0 (0%)	0 (0%)	**6 (2.6%)**
II	18 (50.0%)	17 (47.2%)	1 (2.8%)	0 (0%)	**36 (15.4%)**
III	54 (36.2%)	69 (46.3%)	24 (16.1%)	2 (1.3%)	**149 (63.7%)**
IV	12 (27.9%)	18 (41.9%)	11 (25.6%)	2 (4.7%)	**43 (18.4%)**
Number of evaluable subjects	**88 (37.6%)**	**106 (45.3%)**	**36 (15.4%)**	**4 (1.7%)**	**234**

[a] The baseline NYHA Functional Class was available in all subjects. A total of 234 subjects having their NYHA Functional Class data at 12-month follow-up were eligible for the analysis.

A more conservative analysis of NYHA Class was performed by including subjects excluded from the above analysis because of death or missing data. Table 34 shows the analysis results obtained assuming that their NYHA Class was ≥III.

Table 34. Assessment of NYHA Class at 12 months (conservative analysis)

Included	**Excluded**	**Proportion of subjects with NYHA Class ≤II at 12 months % (n/N)**
Subjects with paired data at baseline and 12 months who completed the study	• Death prior to 12-month follow-up (n = 80) • Surviving subjects with missing data at baseline or 12 months (n = 37)	82.9% (194/234)
Subjects with paired data at baseline and 12 months who completed the study and subjects with missing data • The NYHA Class in subjects with missing data was imputed as ≥III.	• Death prior to 12-month follow-up (n = 80)	71.6% (194/271)
Subjects with paired data at baseline and 12 months who completed the study and subjects who died • The NYHA Class in subjects with missing data was imputed as ≥III.	• Surviving subjects with missing data at baseline or 12 months (n = 37)	61.8% (194/314)
All subjects: • The NYHA Class in dead subjects or subjects with missing data was imputed as ≥III.	None	55.3% (194/351)

6.A.(3).4).(c) SF-36 QOL score

The Quality of Life (QOL) score was analyzed in subjects with evaluable data at both baseline and a post-procedural follow-up time point. A comparison between baseline and 30 days or 12 months showed a significant difference in the Physical Component Summary (PSC) score (physical functioning, physical role, bodily pain, and general health) and the Mental Component Summary (MSC) score (Table 35).

Table 35. Change in SF-36 QOL score (N = 351)

Component	Baseline[a]	30 days[a]	Difference (*P*-value[b])
SF-36 QOL PCS Score Mean ± SD (N)	32.7 ± 8.9 (254)	38.5 ± 9.9 (254)	5.8 ± 9.0 (< 0.0001)
SF-36 QOL MCS Score Mean ± SD (N)	44.7 ± 13.1 (254)	48.6 ± 12.3 (254)	4.0 ± 12.9 (< 0.0001)

Component	Baseline[a]	12 months[a]	Difference (*P*-value[b])
SF-36 QOL PCS Score Mean ± SD (N)	34.0 ± 9.1 (191)	38.8 ± 11.3 (191)	4.8 ± 10.4 (< 0.0001)
SF-36 QOL PCS Score Mean ± SD (N)	44.9 ± 13.5 (191)	49.8 ± 12.2 (191)	5.0 ± 13.0 (< 0.0001)

[a] The analysis included subjects with data at both time points.
[b] Paired t-test

6.A.(3).5) Assessment of degenerative MR and functional MR

6.A.(3).5).(a) Baseline patient characteristic and demographic data and study results by degenerative MR and functional MR

The data were analyzed separately for degenerative MR and functional MR, which have different etiologies. Table 36 shows the baseline characteristics and demographics of the Integrated High Risk Cohort (N = 351) by degenerative MR and functional MR. A significant difference was observed in the following baseline characteristics between subjects with degenerative MR and subjects with functional MR: mean age, proportion of subjects aged >75 years, coronary artery disease, prior percutaneous coronary intervention (PCI), past history of myocardial infarction, prior cardiovascular surgery, diabetes, LVEF, and LVIDs.

Table 36. Baseline characteristics - analysis by MR etiology -

Baseline characteristic	Degenerative MR (N = 105)	Functional MR (N = 246)	*P*-value[a]
Mean age (years), mean ± SD	81.8 ± 9.1 (105)	73.2 ± 10.0 (246)	<0.0001
>75 years of age	81.0% (85/105)	48.4% (119/246)	<0.0001
Female	40.0% (42/105)	38.6% (95/246)	0.8122
Coronary artery disease	74.8% (77/103)	85.4% (210/246)	0.0215
Past history of myocardial infarction	29.5% (31/105)	59.8% (146/244)	<0.0001
Past history of atrial fibrillation	71.6% (73/102)	67.0% (144/215)	0.4399
Past history of stroke	9.5% (10/105)	14.2% (35/246)	0.2955
Diabetes	29.5% (31/105)	43.7% (107/245)	0.0168
Past history of moderate to severe renal disease	26.7% (28/105)	32.1% (79/246)	0.3755
Chronic obstructive pulmonary disease (with or without home oxygen therapy)	28.5% (30/105)	29.0% (71/245)	>0.999
Hypertension	89.5% (94/105)	89.4% (220/246)	>0.999
Prior cardiovascular surgery	50.5% (53/105)	63.8% (157/246)	0.0238
Prior PCI	35.2% (37/105)	56.1% (138/246)	0.0004
Percentage of NYHA Functional Class III/IV	81.9% (86/105)	86.2% (212/246)	0.3301
Mean LVEF (%), mean ± SD	61.0 ± 10.1 (95)	41.7 ± 11.5 (223)	<0.0001
Mean LVIDs (cm), mean ± SD	3.4 ± 0.8 (92)	4.7 ± 1.0 (231)	<0.0001

[a] Non-paired t-test for continuous variables and Fisher's exact test for binary variables

Study results were analyzed. Of 105 subjects with degenerative MR, 83 (79%) achieved acute procedural success with the MitraClip NT System. Of 246 subjects with functional MR, 209 (85.0%) achieved acute procedural success.

Table 37 shows the study results. There was no significant difference between degenerative MR and functional MR. These findings suggested that the MitraClip NT procedure would provide a comparable outcome in high-surgical-risk patients with degenerative MR and patients with functional MR.

Table 37. Analysis by MR etiology

Safety results	Degenerative MR (N = 105)	Functional MR (N = 246)	*P*-value[c]
Mortality at 30 days	6.7% (7/105)	4.1% (10/246)	0.2908
Incidence of major adverse events at 30 days	18.1% (19/105)	19.1% (47/246)	0.8822
Incidence of major adverse events (except for transfusion) at 30 days	8.6% (9/105)	9.3% (23/246)	>0.999
Incidence of major hemorrhagic complications at 30 days	11.4% (12/105)	8.9% (22/246)	0.5445
Incidence of major vascular complications at 30 days	2.9% (3/105)	3.7% (9/246)	>0.999
Mortality at 12 months	23.8% (25/105)	22.4% (55/246)	0.7821
Incidence of major adverse events at 12 months	36.2% (38/105)	38.2% (94/246)	0.8099
Incidence of major adverse events (except for transfusion) at 12 months	26.7% (28/105)	28.5% (70/246)	0.7956
Efficacy results			
Placement rate of MitraClip NT System	95% (100/105)	96% (236/246)	0.7768
Proportion of MR severity <1+ at discharge[a]	48.5% (48/99)	45.1% (102/226)	0.6292
Proportion of MR severity ≤2+ at discharge[a]	80.8% (80/99)	88.1% (199/226)	0.1185
Proportion of MR severity <1+ at 12 months[a]	30.9% (21/68)	39.5% (62/157)	0.2327
Proportion of MR severity ≤2+ at 12 months[a]	85.3% (58/68)	82.8% (130/157)	0.6999
Improvement in LVEDV at 12 months[b]	-19 mL	-18 mL	0.8088
Improvement in LVESV at 12 months[b]	-4 mL	-10 mL	0.0677
Improvement in SF-36PCS at 12 months[b]	6.4	4.1	0.1294
Improvement in SF-36MCS at 12 months[b]	4.3	5.3	0.6233
Percentage of NYHA Functional Class III/IV Baseline → 12 months	78.9% (56/71) → 12.7% (9/71)	83.4% (136/163) → 19.0% (31/163)	0.7930
Rate of hospitalization for cardiac failure per patient-year 12 months pre-procedure → 12 months post-procedure	0.68 → 0.18	0.81 → 0.39	0.1253

[a] The analysis included subjects with data at both baseline and follow-up time points.
[b] Difference in mean between at baseline and 12 months
[c] Non-paired t-test for continuous variables, Fisher's exact test for binary variables, and Bowker method for categorical variables
Note) PCS = Physical Component Summary Score, MCS = Mental Component Summary Score

6.A.(3).5).(b) Comparison of the study results by degenerative MR and functional MR with the results of medical therapy (DUKE data)

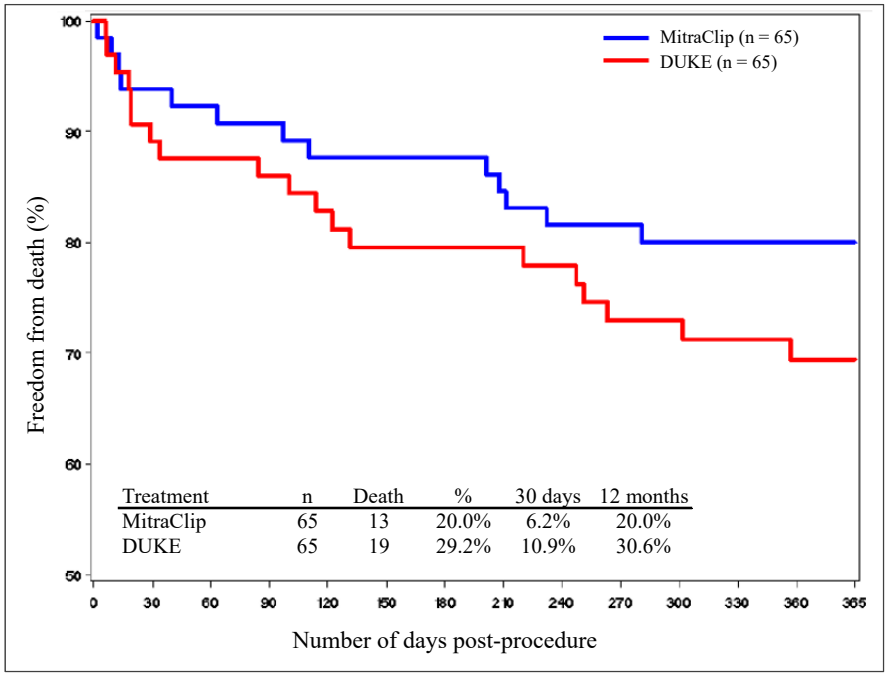
During the preparation of the protocol of the E II HRR study, the study design that included a comparison with literature data was accepted by FDA. However, no suitable publication that could serve as a control was found, thus precluding the inclusion of a literature control group in the study. A control group was newly defined as subjects who had been screened for the E II HRR study to meet the inclusion criteria regarding MR severity (3+/4+) and high risk for surgery, but who were not enrolled in the study. After the completion of subject enrolment in this study, data on freedom from death were collected retrospectively from this control group at days 30 and 12 months [see aforementioned Section "6.A.(2).1) E II HRR study"]. The number of subjects in the control group was, however, as small as 36. In accordance with the direction by FDA, databases available in the US were searched to retrieve data on the outcome of medical therapy in high-surgical-risk patients with symptomatic severe MR that could be compared with the MitraClip group. As a result, the databases

of the Duke Medical Center and the Ohio State University Medical Center were selected as candidates. The database of the Ohio State University Medical Center contained information on high-surgical-risk patients, with no data on MR severity, which would preclude patient matching. Accordingly, the database of the Duke Medical Center, which allowed for propensity score matching for patient characteristics, was chosen for the study.

Patients with symptomatic severe MR who received medical therapy and met the inclusion criteria of the E II HRR study (MR severity 3+/4+ and high risk for surgery) were extracted from this database. Subject enrolment in the E II HRR study was started in [redacted]. To match the time period between the test and control group, approximately [redacted] patients who received medical therapy between [redacted] and [redacted] were selected as candidates from the DUKE database. Finally, 953 patients were identified as high-surgical-risk patients and included in the medical therapy group of the study (DUKE Data).

i) Degenerative MR

A total of 105 subjects with degenerative MR in the Integrated High Risk Cohort and 65 subjects with degenerative MR in the DUKE Data were propensity score matched. As a result, the sample size of each group was 65. The Kaplan-Meier estimate of mortality was 6.2% in the MitraClip group and 10.9% in the medical therapy group at 30-day follow-up, and 20.0% in the MitraClip group and 30.6% in the medical therapy group at 12-month follow-up (Figure 9). The above propensity score matching showed a significant between-group difference in age, past history of PCI, NYHA Functional Class, MR severity, LVEF, and LVID. Propensity score matching when the caliper was 0.25 was also performed to extract 28 subjects per group. The same analysis as above was performed using this subpopulation. The estimated mortality at 12 months in the 0.25 caliper-matched subgroup was 14.3% in the MitraClip group and 26.4% in the medical therapy group.



DUKE Data			
Post-echocardiographic period	**Baseline**	**30 days**	**365 days**
Number of high-risk patients	65	57	39
Number of events	0	7	19
Freedom from death	100.0%	89.1%	69.4%
95% CI		(81.8%, 97.1%)	(58.8%, 81.9%)
Integrated High Risk Cohort			
Post-procedural period	**Baseline**	**30 days**	**365 days**
Number of high-risk patients	65	61	52
Number of events	0	4	13
Freedom from death	100.0%	93.8%	80.0%
95% CI	-	(88.1%, 99.9%)	(70.8%, 90.3%)

Figure 9. Kaplan-Meier survival curve at 12 months
(patients with degenerative MR, 65 vs. 65 in best match group)

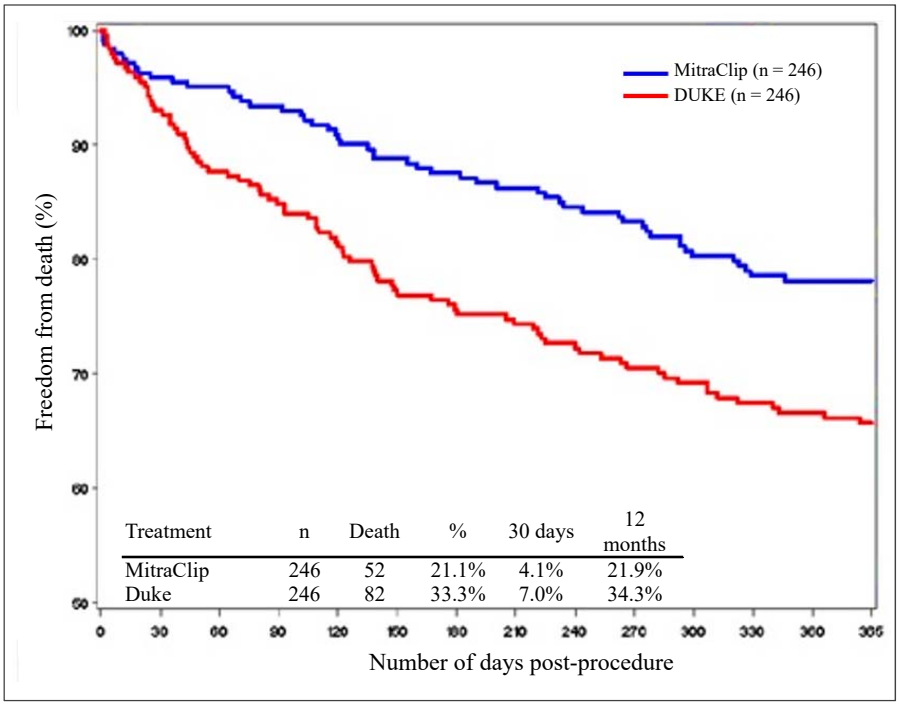
In a Cox proportional hazard model on the survival adjusted for baseline patient characteristics that showed a significant between-group difference, the hazard ratio was 0.63 (95% CI, 0.25-1.61) in 65 subjects in the best match group, suggesting a relative risk reduction of 37% (P = 0.3326). In other subgroups, the MitraClip group also had non-inferior results to the medical therapy group (Table 38).

Table 38. Cox regression analysis of freedom from death at 12 months in match groups (subjects with degenerative MR)

Population	Before adjustment		After adjustment*	
	HR (95% CI)	Log rank *P*-value	HR (95% CI)	*P*-value
All subjects (N = 170)	0.79 (0.44, 1.42)	0.4268	0.78 (0.31, 1.97)	0.601
N = 65, all patients in best match group	0.63 (0.31, 1.27)	0.1907	0.63 (0.25, 1.61)	0.3326
0.25 caliper-matched group (N = 28 vs. matched patients)	0.51 (0.15, 1.74)	0.2705	0.82 (0.19, 3.58)	0.7963

ii) Functional MR

A total of 246 subjects with functional MR in the Integrated High Risk Cohort and 888 subjects with functional MR in the DUKE Data were propensity score matched. As a result, the sample size of each group was 246. The Kaplan-Meier estimate of mortality was 4.1% in the MitraClip group and 7.0% in the medical therapy group at 30-day follow-up, and 21.9% in the MitraClip group and 34.3% in the medical therapy group at 12-month follow-up (Figure 10). The above propensity score matching showed a significant between-group difference in hypertension, atrial fibrillation, MR severity, LVEF, LVID, and STS score. Propensity score matching when the caliper was 0.25 was also performed to extract 199 subjects per group. The same analysis as above was performed using this subpopulation. The estimated mortality at 12 months in the 0.25 caliper-matched group was 19.3% in the MitraClip group and 33.2% in the medical therapy group.



DUKE Data			
Post-echocardiographic period	**Baseline**	**30 days**	**365 days**
Number of high-risk patients	246	226	148
Number of events	0	17	82
Freedom from death	100.0%	93.0%	65.7%
95% CI		(89.9%, 96.3%)	(59.9%, 72.0%)
Integrated High Risk Cohort			
Post-procedural period	**Baseline**	**30 days**	**365 days**
Number of high-risk patients	246	232	180
Number of events		10	52
Freedom from death		95.9%	78.1%
95% CI		(93.4%, 98.4%)	(73.0%, 83.6%)

Figure 10. Kaplan-Meier survival curve at 12 months
(patients with functional MR, 246 vs. 246 in best match group)

In a Cox proportional hazard model on the survival adjusted for the patient characteristics that showed a significant between-group difference, the hazard ratio was 0.56 (95% CI, 0.38-0.82) in 246 subjects

in the best match group, showing a significant difference (P = 0.0031). In other subgroups, the MitraClip group also had non-inferior results to the medical therapy group (Table 39).

Table 39. Cox regression analysis of freedom from death at 12 months in match groups (patient with functional MR)

Population	Before adjustment		After adjustment	
	HR (95% CI)	Log rank *P*-value	HR (95% CI)	*P*-value
All patients (N = 1134)	0.80 (0.59, 1.09)	0.1528	0.68 (0.47, 0.98)	0.0391
N = 246, all patients in best match group	0.58 (0.41, 0.81)	0.0016	0.56 (0.38, 0.82)	0.0031
0.25 caliper-matched group (N = 199 vs. matched patients)	0.52 (0.35, 0.78)	0.0012	0.50 (0.32, 0.78)	0.002

6.A.(3).6) Long-term outcome

Table 40 shows the long-term outcome in the Integrated High Risk Cohort (N = 351) as of [redacted].

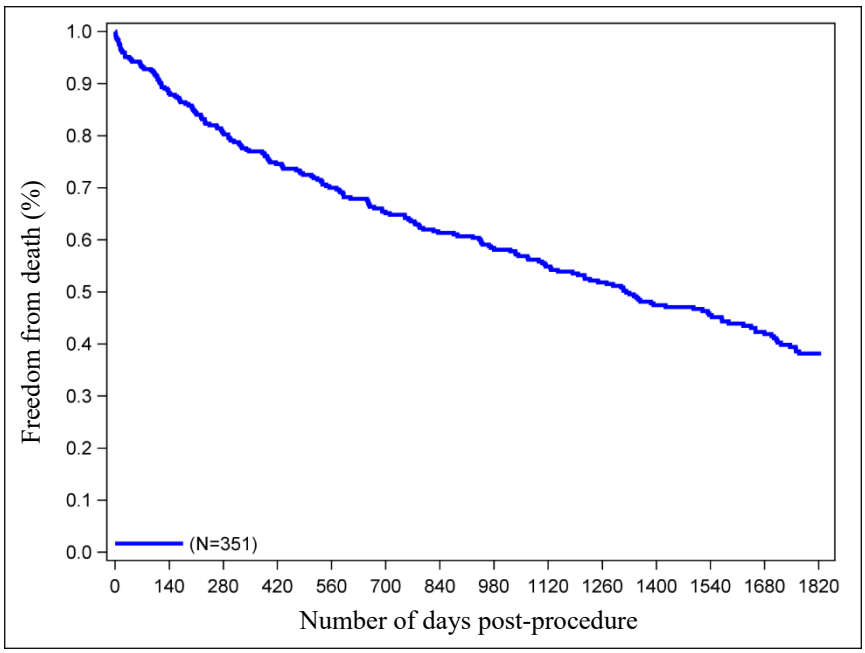
Table 40. Compliance to follow-up visits at each time point through 5 years in the Integrated High Risk Cohort (N=351)

	30-Day	6-Month	12-Month	2-Year	3-Year	4-Year	5-Year
Follow-up visit completed	323	281	247	207	162	126	94
Death before follow-up visit	19	50	80	117	145	172	192
Dropout before follow-up visit	4	9	16	24	32	36	39
No follow-up visit	5	11	8	3	12	17	26

Note) Based on the data locked on [redacted].
The figure in "Death before follow-up" represents the number of subjects who died within the time window of a follow-up visit and failed to undergo the follow-up examination. The figure in "Dropout before follow-up" includes the number of subjects who reportedly died after dropout (1 subject in the E II HRR study reportedly died at 142 days and 1 subject in the Realism HR study reportedly died at 307 days).

6.A.(3).6).(a) Freedom from all-cause death

Freedom from death was 77.0% at 12 months, 64.8% at 2 years, 56.2% at 3 years, 47.1% at 4 years, and 38.1% at 5 years (Figure 11).



	Baseline	30-Day	180-Day	365-Day	730-Day	1095-Day	1460-Day	1825-Day
Number of subjects	351	330	295	258	210	170	131	43
Number of subjects censored	0	4	9	14	22	35	47	115
Number of events	0	17	47	79	119	146	173	195
Freedom from death	100%	95.1%	86.4%	77.0%	64.8%	56.2%	47.1%	38.1%
SE (greenwood)	-	1.2%	1.8%	2.3%	2.6%	2.7%	2.8%	2.8%
95% CI (loglog)	-	[92.3%, 96.9%]	[82.3%, 89.6%]	[72.1%, 81.1%]	[59.5%, 69.7%]	[50.7%, 61.4%]	[41.5%, 52.5%]	[32.6%, 43.7%]

Note) This analysis was based on the data locked on [redacted]. Each follow-up visit had a certain time window. In the Kaplan-Meier analysis, the data were cut off as of the dates shown in the table (at 365 days for 12-month follow-up). One subject died at 142 days and 1 subject died at 307 days after dropout. Both were included in dead subjects in this analysis. For this reason, the total number of deaths within 365 days is equal to the number of deaths at 12 months (deaths in 79 subjects).

Figure 11. Kaplan-Meier estimate of freedom from death at 5-year follow-up (N = 351)

6.A.(3).6).(b) Complications specific to MitraClip NT System

i) Device embolization (defined as the situation where the clip implanted has completely detached from both leaflets and migrated to a site other than the left ventricle or heart)

No device embolization has been reported in 351 subjects included in the Integrated High Risk Cohort analysis at 5-year follow-up.

ii) Single leaflet device attachment (defined as the attachment of one mitral leaflet to the clip)

Single leaflet device attachment (SLDA) was observed in 7 subjects at 12 months (6 at 30 days and 1 after 30 days) and 1 subject after 12 months in 351 subjects in the Integrated High Risk Cohort analysis (Table 41).

Of the 7 subjects with SLDA at 12 months, 2 subjects were switched to mitral valve surgery, and 4 subjects underwent the second MitraClip NT procedure. The remaining 1 subject received no intervention. SLDA after 12 months was reported only in 1 subject (at 18 months). The subject underwent mitral valve replacement at 865 days.

Table 41. Breakdown of interventions for single leaflet device attachment (N = 351)

Breakdown	Proportion of subjects (n/N)		
	At ≤30 days	From >30 days to ≤12 months	At >12 months
Single leaflet device attachment	1.7% (6/351)	0.3% (1/351)	0.3% (1/351)
Mitral valve surgery (N = 3)	0.3% (1/351)	0.3% (1/351)	0.3% (1/351)
Second implantation of MitraClip NT Device (N = 4)	1.1% (4/351)	0.0% (0/351)	0.0% (0/351)
No intervention (N = 1)	0.3% (1/351)	0.0% (0/351)	0.0% (0/351)

Of the 4 subjects who received additional implantation of the MitraClip NT Device, 3 subjects had improvement in MR severity to ≤2+ and 1 subject remained at 3+. Of the 4 subjects, 3 survived at 30-day follow-up after the additional implantation. The remaining 1 subject had improvement in MR severity to 2+ but died from respiratory failure and congestive cardiac failure at 22 days after the additional implantation.

The 3 subjects who underwent mitral valve surgery had successful mitral valve replacement. After the mitral valve replacement, 2 subjects had improvement in MR severity to ≤2+, while the remaining 1 subject had an unknown MR severity because the subject dropped out of the study. All of the 3 subjects survived at 30-day follow-up.

One subject who received no intervention died from cardio-respiratory arrest at 7 days post-MitraClip NT procedure.

iii) Mitral valve stenosis

Mitral valve stenosis was newly reported in 4 subjects from 1 year to 5 years post-procedure. A total of 5 subjects experienced mitral valve stenosis at 5 years. The incidence of mitral valve stenosis in subjects who underwent the MitraClip NT procedure was 1.5% (5 of 336 subjects).

6.A.(4) Study AVJ-514 (study period; [redacted] to [redacted], [redacted])

Study AVJ-514 was a multicenter, single-arm Japanese study conducted in patients with degenerative or functional MR with LVEF ≥30% who were determined to be at prohibitive risk for surgery by a heart team. Its objective was to confirm the reproducibility of the MitraClip NT procedure in Japanese patients. Table 42 shows the primary study design.

Table 42. Study design

Key inclusion criteria	This study enrolled patients aged ≥20 years who met the following inclusion criteria: • Patient with symptomatic and chronic, moderate to severe (3+) or severe (4+) degenerative or functional MR. Their MR severity is assessed based on the Transthoracic Echocardiogram (TTE) within 90 days pre-procedure and the Transesophageal Echocardiogram (TEE) within 180 days pre-procedure. MR severity is confirmed by ECL based on the TTE. The ECL may request a TEE. • Patients with LVEF ≥30% • Patient with NYHA Functional Class II, III, or ambulatory IV • Patients who are considered at high risk for surgery by a cardiac surgeon based on the STS score for predicted mortality risk for mitral valve replacement ≥8% or the presence of any of the defined risk factors.* * The risk factors include the following: Severe porcelain aorta or mobile ascending aorta atheromatous degeneration, post-radiation mediastinum, past history of mediastinitis, functional MR with LVEF <40%, >75 years old with LVEF <40%, re-operation with patent coronary artery bypass grafts, ≥2 prior cardiothoracic surgeries, hepatic cirrhosis, and other surgical risk factors • Patients with a mitral valve area ≥4.0 cm^2 assessed by the ECL. • Patients with the primary regurgitant jet that is non-commissural and is deemed treatable with AVJ-514 by a surgeon in charge of the implantation of AVJ-514. If a secondary jet exists, it must be considered clinically insignificant.
Key exclusion criteria	• Patients with a leaflet anatomy which may preclude the implantation of AVJ-514, proper positioning of AVJ-514 on the leaflets, or adequate reduction in MR. • Patients with LVEF <30%
Primary endpoints	**Primary efficacy endpoints** Acute procedural success **Primary safety endpoint** Freedom from major adverse events* at 30-day follow-up * Major adverse events were defined as the composite of the following endpoint events: Composite of death, stroke, myocardial infarction, renal failure, and non-elective cardiovascular surgery for device- or procedure-related adverse events occurring after femoral vein puncture for transseptal access The results of the primary endpoints (acute procedural success and freedom from major adverse events) of Study AVJ-514 were compared with those in the Integrated High Risk Cohort (N = 351) after propensity score matching. Study AVJ-514 and the Integrated High Risk Cohort had a different definition of major adverse events. The definition of major adverse events for the Integrated High Risk Cohort was adjusted for the definition in Study AVJ-514 to compare the major adverse event data between the two data sets.

Study AVJ-514 was intended to confirm the reproducibility of the implantation procedure of AVJ-514 in Japanese patients. Assuming freedom from major adverse events of 88% and the acute procedural success rate of 70% for this study, it was considered possible to compare the results from 30 subjects in the study and those of the US clinical study based on the following statistical approaches:

1) The precision for defining the difference between the point estimate and the lower limit of the 95% CI is 17% for freedom from major adverse events and 19% for acute procedural success.
2) Freedom from major adverse events is below 80% with a probability of approximately 6%, while acute procedural success is below 60% with a probability of 8%.

This study enrolled 30 subjects who were deemed at high risk for surgery by a cardiac surgeon based on the STS score for predicted mortality risk for mitral valve replacement ≥8% or the presence of any

of the protocol-defined risk factors. No subject discontinued the participation in the study at 30-day follow-up. The ITT population was defined as all the enrolled subjects in whom AVJ-514 was attempted to be implanted.

Of the 30 subjects, 20 had an STS score ≥8% and were enrolled in the study as high-surgical-risk subjects. Of the 30 subjects, 10 had an STS score <8%, and were deemed at high risk for mitral valve surgery by a cardiac surgeon because they had at least 1 of the protocol-defined risk factors for surgery (Table 43).

Table 43. Breakdown of surgical risk factors

Protocol-defined surgical risk factor[a]	AVJ-514 STS score <8% (N = 10)
Functional MR with LVEF <40%	60.0% (6/10)
Age >75 years with LVEF <40%	30.0% (3/10)
Severe porcelain aorta or mobile ascending aorta atheroma	20.0% (2/10)
At least 2 prior cardiothoracic surgeries	10.0% (1/10)
Re-operation with patent coronary artery bypass grafts	10.0% (1/10)

[a] Subjects may be included in more than one category.

The STS Calculator has been continuously revised to reflect the tendency of surgical prognosis. The E II HRR study used the STS Calculator, version 2.52. The mean STS score of all the enrolled subjects was 14.2%. The mean STS score, calculated using version 2.61, revised in 2009, for the same subjects was 10.6%. The change of the STS Calculator from version 2.52 to 2.61 resulted in a reduction of approximately 4% in the STS score even with the same patient characteristics. Given this, changing the STS score from ≥12% to ≥8% is expected not to affect the patient characteristics. Accordingly, the STS score threshold of 8% was selected for the Japanese clinical study.

As shown in Table 44, the mean age was 80.4 ± 7.0 years. Men accounted for 76.7% (23 of 30 subjects) of the study population. The MR severity was 3+ (80.0%) or 4+ (20.0%) in all subjects. Of the 30 subjects, 14 (46.7%) had degenerative MR etiology and 16 (53.3%) had functional MR etiology.

Table 44. Baseline characteristics

Characteristic	(N = 30)
Age, years	
Mean ± SD (N)	80.4 ± 7.0 (30)
>75 years of age, % (n/N)	80.0% (24/30)
Sex, % (n/N)	
Male	76.7% (23/30)
Female	23.3% (7/30)
Comorbidity	
Coronary artery disease (CAD)	40.0 (12/30)
Hypertension	70.0 (21/30)
Hypercholesterolemia	53.3 (16/30)
Angina pectoris	20.0 (6/30)
Past history of stroke	23.3 (7/30)
Past history of myocardial infarction (MI)	26.7 (8/30)
Chronic obstructive pulmonary disease (COPD)	16.7 (5/30)
Diabetes	20.0 (6/30)
Renal disease	66.7 (20/30)
Past history of anemia	60.0 (18/30)
Past history of severe hemorrhage or hemorrhagic disorder	3.3 (1/30)
Prior heart therapy, % (n/N)	
Any surgery	20.0 (6/30)
PCI	26.7 (8/30)
CRT/CRT-D/ICD/permanent pacemaker	20.0 (6/30)
NYHA Class	
I	0.0% (0/30)
II	63.3% (19/30)
III	33.3% (10/30)
IV	3.3% (1/30)
MR severity, % (n/N)	
0: None	0.0% (0/30)
1+: Mild	0.0% (0/30)
2+: Moderate	0.0% (0/30)
3+: Moderate to severe	80.0% (24/30)
4+: Severe	20.0% (6/30)
MR etiology, % (n/N)	
Degenerative MR	46.7% (14/30)
Functional MR	53.3% (16/30)
LVIDs (cm), mean ± SD (N)	4.1 ± 1.2 (30)
LVEF, % (n/N), mean ± SD (N)	50.2 ± 12.8 (30)

6.A.(4).1) Results of primary endpoints

No major adverse events at 30-day follow-up, the primary safety endpoint, was observed. Freedom from major adverse events was achieved in 100% of subjects.

The primary efficacy endpoint “acute procedural success” was achieved in 86.7% (26 of 30) of subjects. Four subjects with acute procedural failure had the device implanted successfully with an MR severity 3+ at discharge.

After propensity matching, 27 subjects with similar baseline characteristics were extracted from both Study AVJ-514 and the Integrated High Risk Cohort. There were no differences in baseline characteristics between the 2 groups.

A between-group comparison of the primary endpoints after the propensity matching showed high performance for acute procedural success and freedom from major adverse events in both groups, with higher point estimates of these outcomes in Study AVJ-514 (Table 45).

Table 45. Comparison of primary endpoints between Study AVJ-514 and Integrated High Risk Cohort after propensity score matching

Primary endpoints	Study AVJ-514 (N=27)	Integrated High Risk Cohort (N=27)	Relative performance (95% CI)	*P*-value
Acute procedural success	85.2% (23/27)	74.1% (20/27)	1.15 (0.88, 1.51)	0.5007
Major adverse events at 30-day follow-up Freedom from major adverse events	100.0% (27/27)	92.6% (25/27)	1.08 (0.97, 1.20)	0.4906

Note) The *P*-values were calculated by an exact test.
Relative performance = Value in Study AVJ-514/Value in the Integrated High Risk Cohort

One subject had SLDA as assessed by the ECL at 30-day follow-up, a secondary endpoint. This subject had acute procedural failure but required no non-elective surgery. No other major adverse events or device-related complications requiring non-elective cardiovascular surgery, such as mitral valve stenosis, device embolization, and iatrogenic atrial septal defect, were reported.

Neither mitral valve surgery nor additional implantation was reported at 30-day follow-up.

Severe hemorrhage (BARC type 3)[1)] was observed in 3 subjects at 30-day follow-up. All events occurred after the implantation of MitraClip NT Device, 2 subjects required transfusion, but all of the subjects recovered without sequela.

The results of the other efficacy and safety evaluation are shown below.

6.A.(4).2) Study site-reported serious adverse events

Serious adverse events reported by the study sites were 1 event of cardiac failure, 1 event of atrial fibrillation with rapid ventricular response, 1 event of bronchopneumonia, 1 event of pneumonia aspiration, 1 event of acute pneumonia, and 1 event of gastrointestinal hemorrhage.

6.A.(4).3) Echocardiographic endpoints

6.A.(4).3).(a) MR severity

The baseline MR severity was moderate to severe (3+) or severe (4+) in all subjects. At discharge and 30-day follow-up, the MR severity improved to mild (1+) or moderate (2+) in 26 of 30 subjects (86.7%).

6.A.(4).3).(b) Cardiac function endpoints

Table 46 shows the results of the left ventricular function parameters at baseline and 30-day follow-up.

Table 46. Changes in left ventricular volume and left ventricular dimension (ITT population)

Left ventricular variables	N	Baseline	30-Day	Difference	*P*-value [a]
LVEDV (mL) Mean ± SD	30	144.1 ± 47.2	130.0 ±37.9	-14.1 ± 27.5	0.0087
LVEDD (cm) Mean ± SD	30	5.7 ± 0.9	5.5 ± 0.8	-0.2 ± 0.5	0.0477
LVESV (mL) Mean ± SD	30	74.1 ± 34.3	68.7 ± 32.2	-5.4 ± 13.5	0.0369
LVESD (cm) Mean ± SD	30	4.1 ± 1.2	4.1 ± 1.2	0.1 ± 0.5	0.5072

[a] Paired t-test
Note) LVEDD = Left Ventricular End Diastolic Dimension, LVESD = Left Ventricular End Systolic Dimension

6.A.(4).4) Clinical endpoints

6.A.(4).4).(a) NYHA Functional Class

The NYHA Class was ≤II in 63.3% (19 of 30) of subjects at baseline and 96.7% (29 of 30) of subjects at 30-day follow-up, showing a significant decrease (Table 47).

Table 47. Summary of matching analysis of NYHA Functional Class at baseline and 30-day follow-up (ITT population)

		AVJ-514 (N=30)		
Test		Baseline	30-day follow-up	*P*-value (Bowker method)
NYHA Functional Class	Class I	0.0% (0/30)	70.0% (21/30)	
	Class II	63.3% (19/30)	26.7% (8/30)	
	Class III	33.3% (10/30)	3.3% (1/30)	
	Class IV	3.3% (1/30)	0.0% (0/30)	
				0.0002

6.A.(4).4).(b) SF-36 QOL score

The Physical Component Summary (PCS) score and Mental Component Summary (MCS) score improved at 30-day follow-up (Table 48).

Table 48. Change in SF-36 QOL score (ITT population)

Variable	Baseline	30-Day	Difference (*P*-value)
SF-36 PCS Mean ±SD (N)	32.2 ± 15.1 (30)	37.5 ± 12.8 (30)	5.3 ± 14.1 (0.0482)
SF-36 MCS Mean ± SD (N)	53.0 ± 9.3 (30)	54.9 ± 7.6 (30)	2.0 ± 10.3 (0.3099)

6.A.(5) Realism HR study (*results from all subjects; study period; [redacted] to [redacted])

The Realism HR study enrolled 628 high-surgical-risk subjects. Table 49 shows compliance to follow-up visits as of [redacted]. The follow-up of the study is ongoing.

Table 49. Compliance to follow-up visits (N = 628)

	30-Day	6-Month	12-Month	3-Year	5-Year
Follow-up visit completed	583	502	438	214	57
Death	30	84	140	248	289
Dropout	5	13	21	46	56
Outside visit window	0	0	0	48	185
Follow-up visit planned	0	0	0	16	12
No follow-up visit	10	29	29	56	29

Note) The protocol was revised in [redacted] to make 2-year and 4-year follow-up visits unnecessary.

Table 50 shows the baseline characteristics and demographics of 628 subjects.

Table 50. Baseline characteristics and demographics (N = 628)

Demographic characteristics	N=628
Age, years	
Mean ± SD (N)	76.7 ± 10.7 (628)
Age >75 years	62.6% (393/628)
Sex, % (n/N)	
Male	59.7% (375/628)
Female	40.3% (253/628)
BMI (kg/m^2), mean ± SD (N)	25.9 ± 8.2 (627)
Atrial fibrillation	70.6% (404/572)
Diabetes	36.3% (227/625)
Myocardial infarction	47.6% (292/613)
Chronic obstructive pulmonary disease (COPD)	
With home oxygen therapy	14.4% (90/626)
Without home oxygen therapy	17.7% (111/626)
None	67.9% (425/626)
Cerebrovascular disease	23.8% (149/627)
NYHA Class, % (n/N)	
I	1.6% (10/628)
II	13.2% (83/628)
III	64.5% (405/628)
IV	20.7% (130/628)
Etiology, % (n/N)	
Degenerative MR	30.4% (191/628)
Functional MR	69.6% (437/628)
Left Ventricular Internal Diameter - systolic (cm), mean ± SD (N)	4.4 ± 1.1 (565)
Left Ventricular Ejection Fraction (%), mean ± SD (N)	47.3 ± 14.0 (542)

Acute procedural success was 82.5% (518 of 628 subjects).

Table 51 shows major adverse events reported at 30 days (or discharge, whichever was later) and 12 months.

Table 51. CEC-adjudicated major adverse events reported at 30 days or 12 days (N = 628)

Event term	Incidence at 30 days % (n/N)	Incidence at 12 days % (n/N)
Death	4.1% (26/628)	22.3% (146/628)
Myocardial infarction	0.5% (3/628)	1.9% (12/628)
Re-operation for failed surgical repair or replacement	0.0% (0/628)	0.0% (0/628)
Non-elective cardiovascular surgery for adverse events	1.3% (8/628)	1.3% (8/628)
Stroke	2.1% (13/628)	2.9% (18/628)
Renal failure	1.1% (7/628)	4.5% (28/628)
Deep wound infection	0.0% (0/628)	0.3% (2/628)
Ventilation >48 hours	3.3% (21/628)	5.7% (36/628)
Gastrointestinal complication requiring surgery	0.0% (0/628)	0.6% (4/628)
New onset of permanent atrial fibrillation	0.2% (1/628)	0.2% (1/628)
Sepsis	1.3% (8/628)	4.8% (30/628)
Transfusion ≥2 units	11.3% (71/628)	19.7% (124/628)
Total	15.6% (98/628)	34.9% (219/628)
Total (excluding transfusion ≥2 units)	8.6% (54/628)	27.4% (172/628)

6.B Outline of the review conducted by PMDA

PMDA's review mainly focused on the following points:

(1) Clinical positioning of the MitraClip NT System
(2) Justification for using the results from the foreign clinical studies as pivotal studies for evaluation of the efficacy and safety of MitraClip NT System in Japanese patients
(3) Efficacy and safety of the MitraClip NT System
(4) Specific risks of the MitraClip NT System
(5) Intended use of the MitraClip NT System
(6) Appropriateness of anticoagulant and antiplatelet therapies
(7) Post-marketing safety measures

6.B.(1) Clinical positioning of MitraClip NT System

The MitraClip NT System was initially expected to provide comparable clinical outcome to surgery. However, on the basis of the results of the E II RCT study and other studies, discussions with FDA or medical experts, and advice from PMDA in the prior assessment consultation, the risk-benefit balance of the MitraClip NT procedure was considered unfavorable in non-high surgical risk patients. Consequently, the applicant submitted the present application after limiting the indication of the MitraClip NT System to patients who are at high risk for mitral valve surgery.

PMDA's view on the clinical positioning of the MitraClip NT System:

Patients with symptomatic MR have a poor prognosis. MR is one of the poor-prognosis factors. Medical therapy alone cannot substantially improve MR. On the other hand, the MitraClip NT procedure leads to a post-operative MR improvement to ≤1+ in most patients, but the outcome is hardly comparable to that in patients who underwent surgery, which has a low risk of re-surgery. In addition, the MitraClip NT System may not always provide a clinically significant improvement in MR (acute procedural success, 77% [137 of 178 subjects] in the E II RCT study, 83.2% [292 of 351 subjects] in the Integrated High Risk Cohort). Although it is inferior to surgery, the MitraClip NT System can physically decrease MR and then decrease the cardiac volume load, resulting in an improvement in the symptoms of cardiac failure. For this reason, it is of clinical significance to make

the MitraClip NT System available in clinical practices as a new treatment option for patients who are at risk for surgery.

6.B.(2) Justification for using the results from the foreign clinical studies as pivotal studies for evaluation of efficacy and safety of MitraClip NT System in Japanese patients

The applicant's explanation about the justification for using the results from the foreign clinical studies for evaluation of the efficacy and safety of the MitraClip NT System in Japanese patients:
The MitraClip NT System is indicated for patients with severe MR, regardless of degenerative or functional MR. Severe MR results in a poor circulatory blood flow, which will impair the functions of other organs. For this reason, MR is defined as a predictor of the prognosis of cardiac failure. Degenerative MR cannot be treated with drugs because it is a disease of the leaflets themselves. Surgery is indicated for severe degenerative MR. Patients with functional MR have enlarged ventricles resulting from other causes. The enlarged ventricles aggravate cardiac failure, secondarily causing regurgitation. Pharmacotherapy for functional MR, therefore, focuses on reduction in cardiac load (e.g., diuretics, angiotensin-converting-enzyme [ACE] inhibitors/angiotensin II receptor blockers [ARB], and β blockers). Patients are treated with cardiotonic drugs, such as digitalis, as necessary. In the early stage of cardiac failure, ARBs may reduce MR. Moderate to severe MR is, however, unlikely to be improved with pharmacotherapy. To treat moderate to severe functional MR, surgery is recommended.

The FDA Advisory Panel reviewed the overall data from patients at high risk for surgery and found no safety concerns. The panel fully supported the benefits of the MitraClip NT procedure in high-surgical-risk patients.

The American College of Cardiology (ACC)/American Heart Association (AHA) Guideline in 2014[2)] classifies isolated valve surgery in patients with functional MR as a Class IIb recommendation, although the guidelines became available after the approval of the MitraClip NT System in the US. The surgery requires cardiac arrest. Although functional MR itself does not increase the risk for surgery (functional MR and degenerative MR not differentiated in the STS Calculator), patients with functional MR generally have a poorer cardiac function and have more comorbidities, both of which contribute to the tendency of higher short- and long-term mortality. Given this, the guideline classifies mitral valve surgery in combination with Coronary Artery Bypass Grafting (CABG) or other surgeries requiring cardiac arrest as a Class IIa recommendation and isolated valve surgery as a Class IIb recommendation. The Japanese guideline[3)] recommends a surgery (Class I) to patients with functional MR when their MR is moderate to severe and symptomatic with LVEF >30% and/or Ds <55 mm. A surgery (Class I) is also recommended to patients with severe and asymptomatic functional MR with LVEF >30% if CABG is indicated. The CHART-1 study,[4)] an epidemiological study in patients with congestive cardiac failure in Japan, demonstrated that patients with moderate to severe congestive cardiac failure have a similar prognosis in Japan and overseas. Considering these findings, the prognosis of medical therapy in the target patient population of the MitraClip NT System is expected to not substantially differ between Japan and overseas. An attempt was made to compare the data from the Integrated High Risk Cohort and data on the outcome of medical therapy in Japan using the database of National Cerebral and Cardiovascular Center (NCCC) of Japan. However, detailed analysis or evaluation of these data was impossible because individual patients' data are not available.

The data of the NCCC show that the rate of freedom from death at 12 months in high-surgical-risk patients with severe MR (n = 53, mean age of 68.2 years) was 82%, which is higher than that (67.2%) in the DUKE Data (n = 351 after matching, mean age of 73.6 years). This difference is attributable to differences in the demographic characteristics of patients between the databases. The rate of freedom from death at 1 year in 953 patients (mean age of 68.5 years) extracted from the database of the US Duke University was 73.8%.

MitraClip NT System does not replace pharmacotherapy, but can offer a treatment option for physically improving MR in a minimally invasive manner to patients who have an inadequate response to a pharmacotherapy. In summary, it is justifiable to evaluate the efficacy and safety of MitraClip NT System in Japanese patients based on the results from the foreign and Japanese clinical studies.

PMDA's view:
No substantial differences between the Japanese and overseas guidelines for the treatment of valvular diseases are seen in their policy for interventional treatment in relation to surgeries that physically reduce MR. The results of the EVEREST II RCT study show that improvement in MR after the MitraClip NT procedure (MR ≤1+) is inferior to that after surgery. However, the physical and therapeutic effects of the MitraClip NT procedure in degenerative MR are expected to be comparable between Japan and the US because regurgitation in patients with degenerative MR is caused by incomplete coaptation due to valvular degeneration. The proportion of ischemic heart disease that causes functional MR may differ between the two countries. In recent years, however, the proportion of cardiac failure due to ischemic heart disease is also increasing in Japan.[5)] The Japanese and US guidelines for the management of cardiac failure[6),7)] show no profound differences in the pharmacotherapy policy, including basic cardiac resynchronization therapy (CRT), or available drugs between the countries. MR Reduction leads to a decrease in the left ventricular volume overload in patients with functional MR whose symptoms of cardiac failure do not improve despite adequate treatment with optimal pharmacotherapy. The therapeutic effect of this treatment will not substantially differ between Japan and the US. Study AVJ-514, conducted in Japan using almost the same inclusion and exclusion criteria as those of the US clinical studies (E II HRR study and Realism HR study), showed the implantation success of 100% (30 of 30 subjects) and the acute procedural success of 86.7% (26 of 30 subjects) without any major adverse event at 30-day follow-up. The outcome of the MitraClip NT procedure was comparable between Japan and overseas. The data indicated no Japan-specific safety concerns. Considering the Japanese and overseas treatment guidelines for chronic cardiac failure and MR, the results of Study AVJ-514, and the condition that the MitraClip NT procedure will be indicated for patients with functional MR only when their left heart function is maintained and their symptoms do not improve with optimal pharmacotherapy, it is possible to evaluate the efficacy and safety of MitraClip NT System in Japanese based on the results of the foreign clinical studies as pivotal studies. As explained by the applicant, the difference in freedom from death at 12 months between the data from the NCCC and the DUKE Data appears to be attributable to differences in the baseline patient characteristics (Table 52). The risk-benefit balance of the MitraClip NT System versus medical therapy will be determined based on comprehensive

assessments of the patient characteristics and other data [see Section "6.(B).(3) Efficacy and safety of MitraClip NT System"].

Table 52. Baseline patient characteristics and freedom from death at 12 months Comparison of data from NCCC, data from Integrated High Risk Cohort, and DUKE Data

	Integrated High Risk Cohort (N = 351)	Matched DUKE Data[a] (N = 351)	DUKE[b] Data (N = 953)	Data from NCCC (N = 53)
Mean age (years) ± SD	75.7 ± 10.5	73.6 ± 11.0	68.5 ± 13.2	68.2 ± 1.9
Male	61.0%	56.4%	48.9%	62.3%
Prior heart surgery	59.8%	55.6%	49.9%	32.1%
Past history of myocardial infarction	50.7%	52.4%	42.8%	13.2%
Past history of atrial fibrillation	68.5%	57.3%	51.7%	45.3%
Past history of stroke	12.8%	13.1%	14.7%	20.8%
Diabetes	39.4%	40.5%	35.5%	26.4%
Renal disease	30.5%	23.9%	18.5%	24.5%
Chronic obstructive pulmonary disease	11.1%	9.1%	7.1%	1.9%
NYHA Functional Class III/IV	84.9%	73.8%	46.6%	56.6%
Functional MR	70.1%	90.3%	93.2%	60.4%
LVEF (%), mean ± SD	47.5 ± 14.2	41.0 ± 11.2	36.7 ± 10.9	47.9%
LVIDs (cm), mean ± SD	4.36 ± 1.11	3.99 ± 1.01	4.2 ± 1.0	5.3 ± 0.2
Freedom from death at 12 months	77.2%	67.8%	73.8%	82%

[a] Patient characteristic data from 351 subjects in the Integrated High Risk Cohort and 351 matched patients extracted from the DUKE Data

[b] Patients extracted from the DUKE database were those who received medical therapy and met the inclusion criteria of the study (MR severity 3+/4+ and high risk for surgery).

6.B.(3) Efficacy and safety of MitraClip NT System

6.B.(3).1) Appropriateness of clinical data used for evaluation

The MitraClip NT System was originally developed for use in surgical candidates. No studies have been conducted as a hypothesis test comparing the MitraClip NT System and medical therapy in high-surgical-risk patients who are included in the proposed indication in the present application. The results of an integrated analysis of the data from the E II HRR study and the Realism HRR study (Integrated High Risk Cohort data) have been used as primary clinical study results. In addition, the database of the Duke University was used for evaluation because no appropriate and sufficient publication reporting the results of medical therapy (the standard of care for high-surgical-risk patients with MR), or natural outcome of MR is available.

The applicant's explanation about the appropriateness of using the DUKE Data as the results of medical therapy to compare the MitraClip NT System:

The database of the Duke University is one of the largest databases of patients with heart diseases. The data regarding the outcome, demographic characteristics, clinical history, and physical examination in all patients who underwent cardiovascular catheterization and heart surgery at the Duke University Medical Center were compiled by the Duke Clinical Research Institute. The data included comprehensive and long-term results from ≥200,000 patients. Patients (approximately [redacted]) registered between [redacted] and [redacted] were searched to correspond to the period of the E II HRR study. Of the patients assessed for MR severity, 953 were at high risk for surgery, which is the proposed indication of MitraClip NT System. Since the patient characteristics differed between the patient population from the DUKE Data and the Integrated High Risk Cohort, propensity score matching was

performed. The data appears to be reliable as they were extracted from the relatively large sample size of 953 patients.

PMDA's view on the appropriateness of the data used for the clinical evaluation of the MitraClip NT System:
The Japanese guideline for valvular treatment classifies surgery as a Class I or IIa recommendation in the treatment of symptomatic severe MR. The clinical significance of correcting the poor coaptation of the leaflets to improve MR has been established. In this review, therefore, the safety of the MitraClip NT System should be evaluated in the view of its specific risks, including residual moderate MR, procedural failure, procedure-related adverse events, different from those of conventional surgeries. Ideally, a clinical study enrolling high-surgical-risk patients, the proposed target patient population, should also have been conducted based on a pre-defined hypothesis. However, the RCT study (E II RCT study) was conducted in non-high surgical risk patients, and there are relatively abundant clinical experience and literature reports regarding the use of the MitraClip NT System in the US and Europe. For these reasons, the clinical evaluation of the MitraClip NT System based on the data from the Integrated High Risk Cohort is reasonable, although the integrated data set is not data from a hypothesis testing study. In addition, no other effective treatment is available for high-surgical-risk patients with symptomatic severe MR, the proposed target patient population. There would be a high medical need for the MitraClip NT System, which can improve MR in a minimally invasive manner. Taken all together, the clinical evaluation of the MitraClip NT System using the data submitted is acceptable.

The Duke University's data that allow propensity score matching are valuable for the evaluation of the MitraClip NT System in patients with cardiac failure with severe MR because the characteristics of such patients appear to give a relatively large impact on their prognosis, though this database includes data from only 1 institution. It is possible to refer to this database along with the known information in publications, etc. The risk-benefit balance of the MitraClip NT System versus medical therapy should be evaluated based on comprehensive data, including other evidence.

6.B.(3).2) Efficacy and safety of MitraClip NT System by MR etiology

While degenerative MR is caused by the degeneration of the valvular or subvalvular tissue, functional MR results from a structural change in the heart due to myocardial disorder. The standard of care, risk for intervention, and the outcome of improvement in MR appear to differ between degenerative MR and functional MR. Both Japanese and overseas guidelines provide separate recommendations for surgery for degenerative MR and functional MR. Hence, the efficacy and safety of interventional treatment with the MitraClip NT System for degenerative MR were evaluated separately from those for functional MR.

6.B.(3).2).(a) Degenerative MR

PMDA's view on the efficacy and safety of the MitraClip NT System in the treatment of degenerative MR in the Integrated High Risk Cohort:
It is clear that cardiac failure in patients with symptomatic degenerative MR results from regurgitation due to degenerative mitral valve disease. There is no effective treatment other than structural repair.

The guidelines for valvular disease treatment available in the US and Europe,[2),8),9)] as well as Japan classify surgery as a Class I recommendation in the treatment of degenerative MR, for which the MitraClip NT System is indicated. From a pathological viewpoint, patients with degenerative MR have symptoms of cardiac failure and decreased cardiac function associated with MR. The clinical significance of correcting the poor coaptation of the leaflets to reduce MR has been established.

The outcomes of 105 subjects with degenerative MR in the Integrated High Risk Cohort showed the acute procedural success of 79% (83 of 105 subjects) after the MitraClip NT procedure. The proportion of subjects with MR severity ≤2+ was 85.3% (58 of 68 subjects) at 12 months. A conservative analysis including subjects excluded from the primary analysis because of death or missing data was performed assuming that their MR severity was ≥3+, and the results showed that 55.2% (58 of 105) of subjects had an MR severity of ≤2+. The proportion of subjects with NYHA Class ≤II increased from 18.1% (19 of 105 subjects) at baseline to 87.3% (62 of 71 subjects) at 12 months. A conservative analysis including subjects excluded from the primary analysis because of death or missing data was performed assuming that their NYHA Class was ≥III, and the results showed that 59.0% (62 of 105) of subjects had NYHA Class ≤II. The rate of hospitalization for cardiac failure per patient-year in 105 subjects improved from 0.68 at baseline to 0.18 at post-procedure. An analysis only in 75 subjects with follow-up data from discharge to 12-month follow-up also showed improvement from 0.67 to 0.13 for the rate of hospitalization for cardiac failure per patient-year. The MitraClip NT System is intended to be used in high-surgical-risk patients, for whom no effective treatment is available. Given this, the MitraClip NT System is effective in the treatment of degenerative MR.

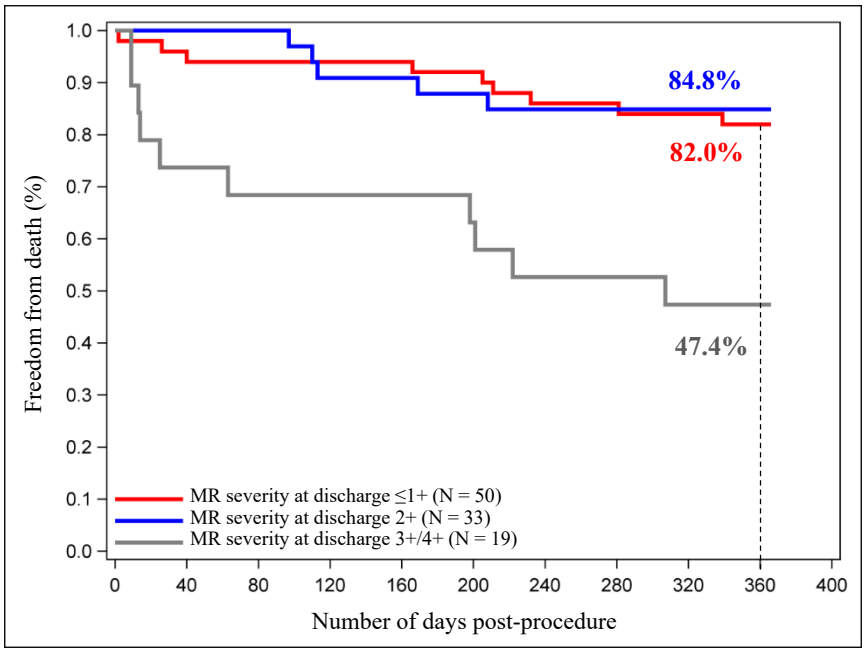
Of 105 subjects with degenerative MR, 25 were dead at 12 months (mortality of 23.8%). The deaths in 7 subjects were adjudicated by CEC to be procedure- or device-related. The conservative mortality, when dropouts and cases of unknown outcome were counted as deaths, was 30.5% (32 of 105 subjects). Although there is some risk for the MitraClip NT procedure, these 105 subjects had advanced ages with the mean age of 81.8 years. In addition, considering the results of mortality with the MitraClip NT procedure versus medical therapy after propensity score matching (MitraClip NT System, 20.0%; medical therapy, 30.6%), the risk for the MitraClip NT procedure is not necessarily higher than that for medical therapy.

The MitraClip NT procedure is associated with acute procedural failure at a certain probability. Its risk-benefit balance should be evaluated based on this risk.

The applicant's explanation about the effect of acute procedural failure (implantation failure and residual MR ≥3+) on the clinical outcome of degenerative MR:
Of 105 subjects with degenerative MR, 83 had acute procedural success. The remaining 22 subjects had acute procedural failure. The baseline patient characteristics showed no significant difference between the subjects with acute procedural success and the subjects with acute procedural failure.

A comparison of the Kaplan-Meier survival curve at 12 months between the subjects with acute procedural success and the subjects with acute procedural failure showed a significant difference in

survival (83.1% of subjects with acute procedural success, 42.9% of subjects with acute procedural failure) ($P < 0.0001$). The effect of residual MR on prognosis was assessed. Freedom from death at 12 months did not differ between subjects with MR severity of 2+ at discharge and subjects with MR severity of 1+ at discharge. Freedom from death at 12 months was significantly higher in subjects with MR severity of ≤1+ or 2+ at discharge than subjects with MR severity of 3+ or 4+ at discharge ($P = 0.0008$, Figure 12).



Follow-up period	Baseline	30-Day	180-Day	365-Day
MR severity at discharge ≤1				
Number of subjects	50	48	46	36
Freedom from event	100%	96.0%	92.0%	82.0%
95% CI	-	[84.9%, 99.0%]	[80.1%, 96.9%]	[66.8%, 90.7%]
MR severity at discharge 2+				
Number of subjects	33	33	29	25
Freedom from event	100%	100%	87.9%	84.8%
95% CI	-	-	[70.9%, 95.3%]	[66.0%, 93.7%]
MR severity at discharge 3+/4+				
Number of subjects	19	14	13	9
Freedom from event	100%	73.7%	68.4%	47.4%
95% CI	-	[47.9%, 88.1%]	[42.8%, 84.4%]	[24.4%, 67.3%]

Figure 12. Kaplan-Meier estimate of freedom from death at discharge by MR severity (≤1+, 2+, and 3+/4+) (degenerative MR)

PMDA asked the applicant to explain the possibility of acute procedural failure increasing the risks of the MitraClip NT System and measures to mitigate those risks because the point estimate of freedom from death at 12 months in 22 subjects with acute procedural failure (42.9%) was lower than that in 65 patients with degenerative MR in the medical therapy group (DUKE Data) (69.4%), though the number of subjects was limited.

The applicant's explanation:
Of 22 subjects with degenerative MR with acute procedural failure (mean age of 83.0 ± 10 years), 5 had implantation failure. Of the 5 subjects, 3 had to be discontinued from the procedure because of

peri-procedural complications (cardiac tamponade, thrombus in the right atrium, and vascular complication). The remaining 2 subjects had unsuccessful implantation for technical reasons (inadequate reduction in MR and insufficient mitral valve area). The procedure was discontinued based on the results of transesophageal echocardiogram (TEE) immediately before implantation. Of 17 subjects who received the implant successfully but had acute procedural failure, 7 had 1 clip implanted. The remaining 10 subjects had 2 clips implanted, without achievement of an MR severity of ≤2+ at discharge. These 17 subjects had various anatomical characteristics of the leaflets. Risk factors could not be identified. Published literature has reported a strong correlation between MR severity and all-cause mortality.[10),11),12),13)] To help achieve acute procedural success, the applicant plans to provide intensive training programs for heart teams and give physicians advice on treatment strategies, including selection of eligible patients, to ensure the reduction of risks to patients and a satisfactory procedural outcome.

PMDA reviewed the details of the 22 subjects with acute procedure failure. Deaths occurred in 11 subjects (mean age of 87.0 years), of whom 7 had cardiac death. Deaths in 5 subjects were adjudicated by the CEC to be procedure- or device-related. Of the 11 subjects, 6 had cardiac or non-cardiac deaths that were adjudicated to be unrelated to the MitraClip NT system. These findings suggest that acute procedural failure is unlikely to be a direct factor to increase the risk of death. As suggested by the analysis of the 5 CEC-adjudicated procedure- or device-related deaths, however, patients with cardiac failure with severe MR, the target patient population of the MitraClip NT System, are high-risk patients with poor prognostic factors, including advanced ages. In such patients, the MitraClip NT procedure may consequently increase the risk of procedure-related complications or death due to intervention, although it is minimally invasive. Cardiac failure in patients with degenerative MR clearly results from MR as the primary disease. Considering that no other effective treatment is available for the target patient population of the MitraClip NT System, its benefits of improving MR outweigh its risks provided that the risk mitigation measures later described [see Sections “6.(B).(4) Specific risks of MitraClip NT System” and “6.(B).(7) Post-marketing safety measures”] are adequately taken.

6.B.(3).2).(b) Functional MR

The applicant has no plan to include functional MR with LVEF <30% in the present application because its supporting clinical data are very limited.

PMDA’s view on functional MR with LVEF ≥30%:

Unlike degenerative MR, functional MR is a disease secondary to underlying factors and is accompanied by left ventricular dysfunction or enlargement. Not all of its problems can, therefore, be solved by controlling MR. The original goal of reducing MR should be improvement of symptoms and control of the progression of left ventricular dysfunction. How the residual MR that may be seen after the MitraClip NT procedure affect the outcome of the disease should be carefully assessed. On the other hand, one of treatment approaches for cardiac failure is reduction in left heart strain. If MR is reduced, even if not eliminated, the left ventricular volume overload can be reduced. This will improve the symptoms of cardiac failure. Patients with ischemic heart disease accompanied by MR reportedly have a poor prognosis compared to patients without MR.[10),14),15),16)] It is of clinical significance to

resolve or reduce MR. In fact, the Japanese and overseas guidelines for treatment of valvular diseases classify surgery as a Class I to IIb recommendation when patients with functional MR who have an intact left ventricular function do not respond to medical therapy even if there is a risk of post-procedural left ventricular dysfunction or recurrence of MR. This means that the MitraClip NT System can be a new treatment option to improve symptomatic MR in patients who are at high risk for surgery, have symptoms that cannot be controlled by medical therapy, and have an intact left ventricular function. To prove this, the risk-benefit balance of the interventional treatment with the MitraClip NT System was assessed.

In the Integrated High Risk Cohort, the proportion of patients with functional MR with LVEF ≥30% who achieved acute procedural success (defined as a reduction in MR to ≤2+) was 84% (155 of 185 subjects). The proportion of subjects achieving MR severity ≤2+ at 12 months was 83% (108 of 130 subjects). A conservative analysis including subjects excluded from the primary analysis because of death or missing data was performed assuming that their MR severity was ≥3+, and the results showed that 58.4% (108 of 185) of subjects had an MR severity of ≤2+. The proportion of subjects with NYHA Class ≤II increased from 13% (24 of 185 subjects) at baseline to 79% (101 of 128 subjects) at post-procedure. A conservative analysis including subjects excluded from the primary analysis because of death or missing data was performed assuming that their NYHA Class was ≥III, and the results showed that 54.6% (101 of 185) of subjects had NYHA Class ≤II. The rate of hospitalization for cardiac failure per patient-year in 185 subjects improved from 0.76 at baseline to 0.34 at post-procedure. An analysis only in 134 subjects with follow-up data from discharge to 12-month follow-up also showed improvement from 0.63 to 0.29 for the rate of hospitalization for cardiac failure per patient-year. Although the data are from a small number of patients who were surgical candidates, the 5-year long-term results in evaluable patients with functional MR in the MitraClip group in the E II RCT study showed that 85.7% (18 of 21) of subjects had an MR severity of ≤2+.

PMDA asked the applicant to explain the details of concomitant pharmacotherapies in patients with functional MR because these therapies may affect the clinical outcome of patients. As shown in Table 53, optimal pharmacotherapies (ACE inhibitor or ARB + β blocker + diuretic) and their breakdown showed no substantial change between before and after the procedure.

Table 53. Pharmacotherapies for cardiac failure in subjects with functional MR with LVEF ≥30% (of 185 subjects, 143 subjects with data at both baseline and 12 months)

Category of pharmacotherapy	Baseline	12-month follow-up	Difference	*P*-value (McNemar test)
ACE inhibitor/ARB	65.7% (94/143)	65.7% (94/143)	-0.0% (-11.7%, 11.7%)	1.0000
β blocker	83.9% (120/143)	81.1% (116/143)	-2.8% (-6.7%, 12.3%)	0.5034
Diuretic	88.1% (126/143)	83.9% (120/143)	-4.2% (-4.5%, 12.9%)	0.2863
Optimal medical therapy (3 of the drugs above)	49.0% (70/143)	46.2% (66/143)	-2.8% (-9.5%, 15.1%)	0.6076
2 of the drugs above	41.3% (59/143)	41.3% (59/143)	-0.0% (-12.1%, 12.1%)	1.0000
1 of the drugs above	8.4% (12/143)	9.8% (14/143)	1.4% (-8.8%, 6.0%)	0.7744

PMDA's view:

A relatively high proportion of the subjects with functional MR with LVEF ≥30% achieved and maintained reduced MR and improved symptoms, which are the therapeutic concepts of the MitraClip

NT System. These findings indicate the efficacy of the MitraClip NT System. On the other hand, of 185 subjects with functional MR with LVEF ≥30% who received MitraClip NT Device, 38 were dead at 12 months (mortality of 21.0%, 38 of 185 subjects). The conservative mortality, when dropouts and cases of unknown outcome were counted as deaths, was 29.7% (55 of 185 subjects). Of the deaths in 38 subjects, 11 cases were adjudicated by the CEC to be procedure- or device-related, suggesting a certain level of risk for the MitraClip NT System. MR is a poor prognostic factor, but not a primary etiology. PMDA asked the applicant to explain the risk-benefit balance of the MitraClip NT System in high-surgical-risk patients with cardiac failure accompanied by functional MR with LVEF ≥30% based on a comparison with the standard medical therapy, accumulated clinical evidence, and other data.

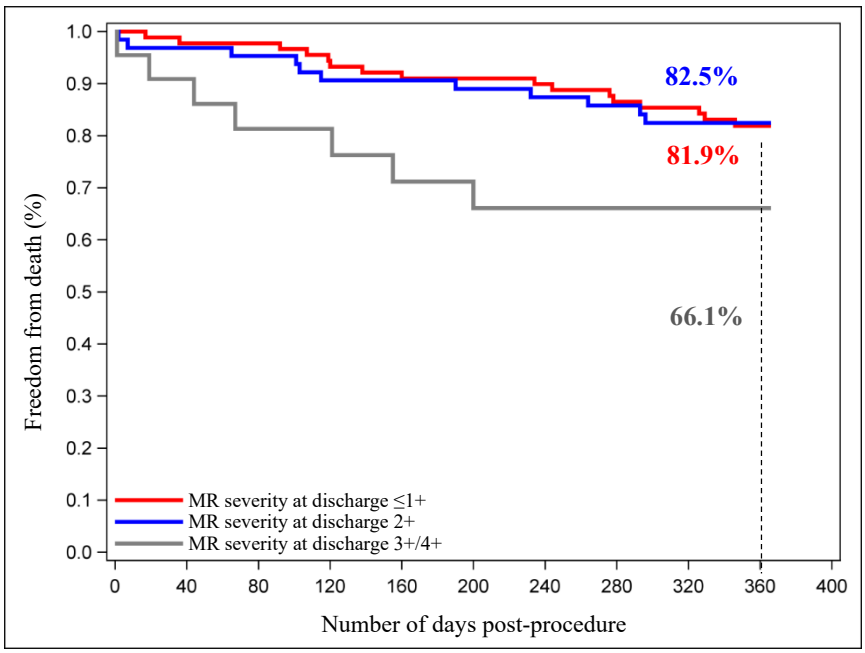
The applicant's explanation:
Even the conservative analysis counting cases of unknown outcome as death demonstrated that the morality (29.7%) at 410 days in the MitraClip group was comparable to the morality (34.3%) at 365 days in the medical therapy group in the DUKE Data. Pharmacotherapies are not expected to profoundly improve MR except for mild MR. On the other hand, ≥50% of the subjects in the MitraClip group maintained MR severity ≤2+ at 12 months, as shown even by the conservative analysis including subjects excluded from the primary analysis because of death or missing data assuming that their MR severity was ≥3+. A similar analysis by the NYHA Class also showed that ≥50% of the subjects maintained the NYHA Class ≤II at 12 months. Both proportions of subjects profoundly increased from baseline. Even the results of the conventional analysis support the efficacy and safety of the MitraClip NT procedure.

Giannini et al.[17] reported the results of a comparison between the MitraClip NT procedure and medical therapy in patients with severe functional MR registered continuously at the same medical institution during the same period. Although the sample size is limited (60 in the MitraClip group, 60 in the medical therapy group), the proportion of patients who achieved freedom from death at 12 months was 89.7% in the MitraClip group and 64.3% in the medical therapy group. Rossi et al.[12] researched the prognosis in 1,256 patients with functional MR and reported that the proportion of patients with severe MR who achieved freedom from death at 1 year was approximately 80% for non-ischemic patients and approximately 75% for ischemic patients. This report defined severe MR as RV of >30 mL, which corresponds to ≥2+ in the definition of the clinical studies of the MitraClip NT System. The mean age of patients with severe MR was 69 years, which is lower than that (74 years) in 185 patients with functional MR with LVEF ≥30%. This finding also supported the use of the DUKE Data, which show that freedom from death was achieved in slightly under 70% of high-surgical-risk patients, the target patient population of the MitraClip NT System, who had received medical therapy.

The MitraClip NT System is not intended to replace medical therapy. The combination of the MitraClip NT System and medical therapy is expected to provide additional benefits without a profound risk. Although only limited data are available regarding freedom from death in the target patient population in Japan, the use of the MitraClip NT System can provide an additional improvement even in patients with a good outcome of medical therapy.

PMDA asked the applicant about the evaluation of the risk-benefit balance of the MitraClip NT procedure based on the risk for acute procedural failure because the MitraClip NT procedure is associated with acute procedural failure at a certain probability.

The applicant's explanation about the effect of procedural failure and residual MR on the clinical outcome of functional MR:
Acute procedural success was achieved in 84% (155 of 185) of subjects with functional MR with LVEF ≥30%. The baseline characteristics of subjects with functional MR with LVEF ≥30% who achieved acute procedural success were similar to those of subjects who had acute procedural failure. The Kaplan-Meier estimate of the freedom from death at 12-month follow-up in the subjects with functional MR with LVEF ≥30% was used for comparison between the acute procedural success group and the acute procedural failure group. The proportion of subjects achieving freedom from death at 12-month follow-up was 81.7% in the acute procedural success group and 68.5% in the acute procedural failure group. The effect of residual MR on prognosis was assessed. As in subjects with degenerative MR, the proportion of subjects achieving freedom from death at 12 months was similar in subjects with functional MR with MR severity at discharge of 2+ and those with MR severity at discharge of 1+. The proportion of subjects achieving freedom from death at 12 months was higher in subjects with functional MR with MR severity of 2+ or 1+ at discharge than in those with MR severity of 3+ or 4+ at discharge (P = 0.1255, Figure 13).



Follow-up period	Baseline	30-Day	180-Day	365-Day
MR severity at discharge ≤1				
Number of subjects	89	88	81	64
Freedom from event	100%	98.9%	91.0%	81.9%
95% CI	-	[92.3%, 99.8%]	[82.8%, 95.4%]	[71.4%, 88.8%]
MR severity at discharge 2+				
Number of subjects	65	62	57	43
Freedom from event	100%	96.9%	90.6%	82.5%
95% CI	-	[88.1%, 99.2%]	[80.2%, 95.7%]	[69.1%, 90.4%]
MR severity at discharge 3+/4+				
Number of subjects	22	19	14	13
Freedom from event	100%	90.9%	71.2%	66.1%
95% CI	-	[67.3%, 97.7%]	[46.0%, 86.2%]	[41.1%, 82.5%]

Figure 13. Kaplan-Meier estimate of freedom from death at discharge by MR severity (≤1+, 2+, and 3+/4+) (functional MR with LVEF ≥30%)

PMDA's view:

Although the number of subjects with functional MR with LVEF ≥30% who had acute procedural failure was limited (30 subjects), the point estimate of the mortality at 12 months was higher in patients with acute procedural failure (30% [9 of 30 subjects]) than in patients with acute procedural success (19% [29 of 155 subjects]). The mortality at 1 year in patients with functional MR who received medical therapy from the patient characteristic-matched DUKE Data was 34.3%. The mortality was reportedly 20% to 36% in some publications, although their patient characteristics might be different from those in the clinical studies.[12),17)] In summary, procedural failure with the MitraClip NT System does not necessarily increase profoundly the risk of death. Of deaths occurring in 9 subjects after acute procedural failure, 5 cases were adjudicated by the CEC to be procedure- or device-related. In high-surgical-risk patients with poor prognosis, the target patient population of the MitraClip NT System, procedure-related complications and intervention with the MitraClip NT System may affect their prognosis.

Patients with symptomatic functional MR have a poor prognosis despite the adequate treatment of for the primary disease including appropriate medical therapy. There is no effective treatment available for

high-surgical-risk patients. The MitraClip NT procedure has been shown to be effective in improving MR severity and clinical symptoms in high-surgical-risk patients with functional MR and may improve their prognosis, although the treatment is associated with certain risks, such as insufficient MR reduction. Taken together with the comments from the Expert Discussion, the benefits of the MitraClip NT System outweigh its risks in patients for whom no other effective treatments are available, as described above, provided that the risk mitigation measures later described [see Sections "6.(B).(4) Specific risks of MitraClip NT System" and "6.(B).(7) Post-marketing safety measures"] are sufficiently taken.

6.B.(4) Specific risks of MitraClip NT System

6.B.(4).1) Acute procedural failure

The applicant has included the following anatomical features ineligible for the MitraClip NT procedure in the "Warning" section of the instructions for use:

- Severe calcification in the grasping area of the leaflets
- Severe calcification in the valvular and/or subvalvular tissue, such as the tendinous cords
- Severely limited mobility of the posterior leaflet
- Laceration or perforation in the grasping area
- Flail gap ≥10 mm, flail width ≥15 mm, or both
- Coaptation length <2 mm
- Intracardiac mass
- Mitral valve area <4 cm^2
- The primary regurgitant jet outside the A2 and P2 scallops and/or clinically significant secondary jet

PMDA asked the applicant to explain, based on the latest knowledge, whether there is any patient's pre-procedural condition that precludes the MitraClip NT procedure, other than the above anatomical features.

The applicant's response:

There are various and complex reasons why MR with a severity of ≥3+ remains after successful implantation of the MitraClip NT Device. No anatomical conditions, other than the above, have been identified as a predictive factor of residual MR. A publication reported that accumulated experience with the use of the MitraClip NT System increased the odds of procedural success,[18)] which may be because more eligible patients can be selected based on experience. The acute procedural success with the MitraClip NT System is approximately ≥80%. Considering that the target patient population is high-surgical-risk patients for whom no other treatment options are available, this rate is acceptable clinically. In fact, ≥40,000 patients have undergone the MitraClip NT procedure to date.

PMDA's view:

To minimize the possibility of acute procedural failure, the following treatment approaches should be taken based on the limitations of this treatment: Eligible patients should be selected based on pre-procedural examinations, and appropriate decisions should be made on whether to use additional clips and whether to discontinue the procedure itself based on MR severity assessment during a

peri-operative attempt to grasp the leaflets. Currently, predictive factors for acute procedural failure have not been clearly identified. The supportive measures for the MitraClip NT procedure, including training programs, have been continuously updated based on accumulated knowledge since the beginning of the development of this product. The acute procedural success rate with the MitraClip NT System has reportedly increased over time. The Japanese clinical study, which was conducted by the investigators who had no experience of using the MitraClip NT System, showed a relatively high acute procedural success rate (86.7%) (Table 54). If physicians acquire knowledge about the MitraClip NT procedure and necessary techniques through technical support from proctors (instructors) or training, a certain rate of acute procedural success can be ensured in Japan [see Section "6.(B).(7) Post-marketing safety measures"].

Table 54. Acute procedural success rate in each study

Study	Enrollment period	Acute procedural success rate
E II HRR study (N = 78)	[redacted] to [redacted]	71.8% (56/78)
Integrated High Risk Cohort (N=351)	[redacted] to [redacted]	83.2% (292/351)
Study AVJ-514 (N = 30)	[redacted] to [redacted]	86.7% (26/30)

On the other hand, acute procedural failure may occur at a certain probability because of the characteristics of the MitraClip NT System. In the case of acute procedural failure, intervention with the MitraClip NT System, although it is minimally invasive, may increase the risks of complications and death compared with continuing medical therapy. Not only treating physicians but also recipient patients should be fully informed of these potential risks for the MitraClip NT System. PMDA instructed the applicant to provide relevant information through training programs and the instructions for use. The applicant agreed.

6.B.(4).2) Worsening of MR severity in subjects with acute procedural success during follow-up period

Of 292 subjects with acute procedural success in the Integrated High Risk Cohort (N = 351), 33 had worsening MR in the distal period. Of the 33 subjects, 1 underwent surgery (due to SLDA), 6 received an additional clip(s) (3 subjects due to SLDA, 3 subjects due to other reasons), and 26 received no intervention. Of 26 subjects with acute procedural success in Study AVJ-514, 1 had worsening MR at 30 days. This subject received no intervention.

PMDA's view:

Since the causes for worsening MR in these subjects during the follow-up period remain unclear, both physicians and patients should understand the limitations of the MitraClip NT procedure prior to the treatment. PMDA instructed the applicant to provide users with relevant information through the instructions for use, training programs, and other materials. The applicant agreed. SLDA occurred in a certain proportion of subjects. This adverse event is discussed later in Section "6.B.(4).3) Single leaflet device attachment."

6.B.(4).3) Single leaflet device attachment

Table 55 shows the incidence of SLDA in each clinical study.

Table 55. Incidence of SLDA in each study

Study	Enrollment period	Incidence of SLDA
E II Roll-In study[a]	[redacted] to [redacted]	10.9% (6/55)
E II RCT study[b]	[redacted] to [redacted]	6.3% (10/158)
E II HRR study[c]	[redacted] to [redacted]	1.3% (1/75)
Integrated High Risk Cohort (N=351)[d]	[redacted] to [redacted]	2.3% (8/351)
Study AVJ-514[e]	[redacted] to [redacted]	3.3% (1/30)

[a] The 5-year results of the E II Roll-In study
[b] The 5-year results of the E II RCT study
[c] The 5-year results of the E II HRR study
[d] The 5-year results of the Integrated High Risk Cohort
[e] The 30-day results of Study AVJ-514, based on the assessment by ECL (no SLDA reported from the study sites)
Note) The denominator included only subjects who had at least 1 clip implanted.

The applicant's explanation:
The most likely primary cause of SLDA was the insufficient attachment of either side of the clip of the MitraClip NT System to the leaflet during the procedure. The instruction manual of the MitraClip NT System was revised in [redacted] to add an improved method for assessment of clip attachment to the leaflet. In addition, technical training was provided to physicians to ensure the complete attachment of both sides of the clip of the MitraClip NT System to the leaflets. As a result, the incidence of SLDA decreased (Table 55).

PMDA's view:
The incidence of SLDA is 2% to 3% based on the recent clinical data. In Study AVJ-514, 1 event (3.3% [1 of 30 subjects]) was reported. Considering these findings, PMDA agreed with the applicant's explanation that the current measures, including training programs, are effective in reducing the risk of the event. However, SLDA requires re-treatment, either surgery or implantation of an additional clip(s). Whether the risk mitigation measures are sufficient in Japan, where physicians have little experience with the use of the MitraClip NT System, should be determined as necessary based on the long-term data of the clinical study submitted and the results of a use-results survey. Accordingly, Approval Conditions 2 and 3 should be imposed.

6.B.(4).4 Implantation of multiple clips and mitral valve stenosis
The risk for implanting additional clips and the possibility of the contribution of such additional clips to acute procedural success need to be clarified. PMDA asked the applicant to explain the necessity of limiting the number of clips to be implanted in the post-marketing setting.

The applicant's explanation:
The protocol of the E II study allowed for implantation of additional clips in the case of insufficient MR reduction after implantation of 1 clip. Prior to additional implantation, whether subjects had a sufficient mitral valve area was to be determined to prevent mitral valve stenosis from occurring. As shown in Table 56, approximately 60% of the subjects in the E II study required 1 clip to complete the treatment, while the remaining approximately 40 subjects required 2 clips.

In the Integrated High Risk Cohort, mortality and the incidence of the major adverse events showed no difference between subjects with 1 clip and subjects with 2 clips. Although the latter subjects had a prolonged duration of the procedure, additional implantation is not associated with safety concerns. For this reason, physicians rather tend to place 2 clips. As a result, multiple clips were implanted in

45.6% (162 of 355) of subjects in the late phase of the Realism HR study and 70.0% (21 of 30) of subjects in the Japanese study. However, there is no evidence that implantation of multiple clips ensures the reduction of residual MR. Implantation of multiple clips may increase the risk of mitral valve stenosis. The maximum number of clips to be implanted must be 2 in principle.

Table 56. Number of clips implanted in each study

Study	0	1	2	3
E II HRR study (N = 78)	3.8% (3/78)	59.0% (46/78)	37.2% (29/78)	-
Integrated High Risk Cohort (N=351)	4.3% (15/351)	57.3% (201/351)	38.5% (135/351)	-
AVJ-514 (N = 30)	0.0% (0/30)	30.0% (9/30))	63.3% (19/30))	6.7% (2/30))

Table 57 shows the incidence of mitral valve stenosis in each clinical study.

Table 57. Incidence of mitral valve stenosis in each clinical study

Clinical study	Incidence
E II HRR study (N = 78)[a]	2.7% (2/75)
Integrated High Risk Cohort (N=351)[b]	1.5% (5/336)
Study AVJ-514[c]	0.0% (0/30)

[a] The 5-year results of the E II HRR study
[b] The 5-year results of the Integrated High Risk Cohort
[c] The 30-day results of Study AVJ-514
Note) The denominator included subjects who had at least 1 clip implanted.

PMDA's view:

Considering the incidence of mitral valve stenosis of 0% to 2.7% in each clinical study, the applicant's explanation is generally acceptable. However, patients with acute procedural failure have a poor prognosis. Additional implantation of >2 clips may be required depending on the peri-procedural condition. The available clinical data regarding the implantation of >2 clips are too sparse to fully verify its efficacy and safety. PMDA instructed the applicant to include this information in the instructions for use and other materials to ensure that users carefully determine the use of multiple clips. The applicant agreed. PMDA also considers it necessary to collect information on patients who receive >2 clips in the post-marketing setting through a use-results survey, etc. to verify its safety, including the incidence of mitral valve stenosis (Approval Condition 2).

6.B.(4).5) Atrial septal defect

Table 58 shows the incidence of atrial septal defect requiring repair in each clinical study.

Table 58. Incidence of atrial septal defect requiring repair in each study

Study	30 Days	12 Months
E II HRR study (N = 78)	2.6% (2/78)	2.6% (2/78)
Integrated High Risk Cohort (N=351)	1.7% (6/351)	3.1% (11/351)
Study AVJ-514 (N = 30)	0% (0/30)	-

The applicant's explanation about this adverse event:

The incidence of atrial septal defect was 0% to 2.6% at 30 days and 2.6% to 3.1% at 12 months. Atrial septal defect occurred in 11 subjects in the Integrated High Risk Cohort, and all of the cases were percutaneously repaired successfully. None required thoracotomy for repair. Registry data from the National Cardiovascular Data Registry (NCDR) reported by Ailawadi, et al.[19] show the incidence of atrial septal defect requiring repair of 1.6% both in 2014 (n = 1,023) and 2015 (n = 3.362). Alkhouli et

al.[20] analyzed the results of 8 studies involving different types of atrial septal puncture (N = 460). They reported the incidence of iatrogenic residual atrial septal defect during the follow-up period of 0% to 50% and its strong correlation with the size of atrial septal catheters. Given this, this incidence is acceptable because the target patient population is high-surgical-risk patients for whom no other treatment options are available.

PMDA's view:
The clinical data show the incidence of atrial septal defect requiring repair is 2% to 3%. In Study AVJ-514, this event was not reported at 30 days. The incidence of atrial septal defect does not profoundly differ between the MitraClip NT procedure and other therapeutic procedures involving atrial septal puncture. In addition, all of the cases were successfully repaired percutaneously. For these reasons, the applicant's explanation is acceptable.

6.B.(4).6 Surgery as treatment option after implantation of MitraClip NT System

The data locked as of [redacted], [redacted] from the Integrated High Risk Cohort (N = 351) including subjects who were at high risk for surgery showed that 14 subjects underwent mitral valve surgery after implantation of the MitraClip NT Device (mitral valve replacement in 12 subjects and valvuloplasty in 2 subjects).

The possible causes for mitral valve replacement during conversion to surgical intervention after implantation of the MitraClip NT Device are difficulty in removing the clip(s), proliferation of the clip tissue, or injury to the leaflet(s). The MitraClip NT System is indicated for high-surgical-risk patients. Nevertheless, once the patient's general condition improves, the patient may be able to undergo surgery. Some patients may be unable to undergo valvuloplasty after implantation of the MitraClip NT Device. This possibility should be fully considered prior to the use of the MitraClip NT System. PMDA instructed the applicant to provide users with relevant information through training programs, the instructions for use, and other materials. The applicant agreed.

6.B.(4).7 Long-term safety

PMDA's view:
On the basis of the 5-year results from the E II RCT study and the E II HRR study, albeit small sample size, there are no significant concerns about the long-term safety of the MitraClip NT System because the incidence of events including SLDA, mitral valve stenosis, MR worsening, implantation of additional clips, and conversion to surgical intervention has not tended to increase substantially over time. At this time point, however, the 5-year results from an only limited number of subjects are available. The applicant should periodically review the long-term results of the clinical studies submitted and other data, and provide healthcare professionals with relevant information or take risk mitigation measures as necessary (Approval Condition 3).

6.B.(5) Intended use or indication of MitraClip NT System

PMDA's view:
Taken together with the comments from the Expert Discussion, the selection of eligible patients and the proper use of the device are necessary to assure the efficacy and safety of the MitraClip NT System.

Pathological conditions in which the efficacy and safety of the MitraClip NT System are not currently established should be clarified. Patients meeting the following descriptions should be excluded from the proposed intended use "Treatment of mitral regurgitation in patients with symptomatic severe mitral regurgitation (MR severity 3+ or 4+) with a left ventricular ejection fraction of ≥30% who are at high risk for open-heart surgery."

- No studies involving patients with functional MR who have not been adequately treated with optimal medical therapy for cardiac failure have been conducted to compare the results of medical therapy and those of the interventional treatment with the MitraClip NT System. The MitraClip NT System is not intended to replace medical therapy. The risk-benefit balance of the MitraClip NT System has not been assessed in patients whose cardiac failure symptoms are well controlled by medical therapy.
- Acute worsening of MR is often accompanied by various pathological conditions, such as chordal rupture, which require emergency response. In such case, the efficacy and safety of the MitraClip NT System have not been established.
- The target patient population in the present application is patients with conserved cardiac function. The present application does not include patients whose heart dose not function without an inotropic support (catecholamine) or assisted circulation. There is only limited experience with the use of the MitraClip NT System in such a patient population.

PMDA instructed the applicant to add the following information to the proposed "Intended Use or Indication." The applicant agreed.

Intended Use or Indication

Treatment of mitral regurgitation in patients with symptomatic severe mitral regurgitation (MR severity 3+ or 4+) with a left ventricular ejection fraction of ≥30% who are at high risk for open-heart surgery, except for patients who:

- Have functional mitral regurgitation that has not been adequately treated with optimal medical therapy recommended by Japanese guidelines,
- are experiencing acute worsening,
- have dependence on inotropic drugs (catecholamine), or
- are using assisted circulation.

The applicant's explanation about the clinical positioning of CRT and the MitraClip NT System:

There is no standard single algorithm in choosing the MitraClip NT System or CRT. In the US, either device is chosen on a case-by-case basis according to the US guidelines.[2),21)] The protocol of a currently ongoing US study that compares the MitraClip NT System and medical therapy defines CRT as the optimal therapy. The protocol specifies the use of CRT prior to enrollment in the clinical study unless it is not contraindicated.

PMDA's view:

Since there are no sufficient evidence-based criteria to choose either CRT or the MitraClip NT System, it is essential to ensure that the heart team makes an appropriate decision depending on the conditions

of individual patients. PMDA instructed the applicant to provide users with relevant information through training programs, the instructions for use, and other materials. The applicant agreed.

6.B.(6) Appropriateness of anticoagulant and antiplatelet therapies

Severe hemorrhage was reported in 3 subjects in Study AVJ-514. Severe hemorrhagic complications was reported in 34 subjects at 30 days and 41 subjects at 12 months in the Integrated High Risk Cohort. PMDA asked the applicant to explain the cause of the high incidence of hemorrhagic complications, as well as anticoagulant and antiplatelet therapies recommended in Japan based on the cause.

The applicant's explanation:

Anticoagulants and antiplatelets after the MitraClip NT procedure in Study AVJ-514 were selected by the investigator or subinvestigator according to the following recommendations:

1. The anticoagulant therapy given to the subject prior to the procedure, if any, should be resumed at an appropriate dose after the procedure. If an anticoagulant is administered for a long period, aspirin and ticlopidine are not recommended unless they are specifically indicated for the subject's condition.
2. If any anticoagulant is not administered for a long period, the use of ticlopidine and/or aspirin (81 mg/day) for ≥6 months is recommended. Aspirin can be used prior to or immediately after the implantation of AVJ-514 according to the standard method of each study site, if deemed necessary by the investigator or subinvestigator.

Of the 41 subjects with severe hemorrhage at 1 year in the Integrated High Risk Cohort, 23 (56.1%) had a history of atrial fibrillation. The hemorrhage in these 23 subjects occurred at the access site in 9 subjects, in the chest wall/thorax during the procedure in 6 subjects, and in the gastrointestinal tract in 5 subjects, including some TEE-related event. The remaining 3 subjects experienced intracranial hemorrhage, hypotension, and hemorrhage of unknown site. Of the 41 subjects with severe hemorrhage, 7 (17.1%) had peptic ulcer. Of them, 3 subjects had a history of atrial fibrillation. The severe hemorrhage in these 7 subjects occurred at the access site in 3 subjects, in the gastrointestinal tract in 2 subjects, in the chest wall/thorax during the procedure in 1 subject, and at an unknown site in 1 subject. Of the 41 subjects with severe hemorrhage by Year 1, 31 subjects (73.2%) were on anticoagulant therapy, antiplatelet therapy, or both at the onset of hemorrhage.

The use of anticoagulant and antiplatelet therapies should be determined taking into consideration the health condition of each patient. In general, anticoagulant therapy is used for patients with atrial fibrillation. Whether antiplatelet therapy should be administered alone or in combination with anticoagulant therapy after the MitraClip NT procedure should be determined by physicians on an individual patient basis.

PMDA's view:

To reduce thrombotic adverse events related to the MitraClip NT procedure, some antiplatelet therapy should be administered to patients. However, the treatment is often associated with severe hemorrhage. The use of concomitant antiplatelet therapy should be carefully considered especially in patients requiring anticoagulant therapy because of atrial fibrillation. The applicant claims that pre- and

post-procedural anticoagulant and antiplatelet therapies should be selected on an individual patient basis. The applicant's opinion is generally understandable. Currently, there is not necessarily enough evidence supporting any criterion to select optimal anticoagulant or antiplatelet therapy. PMDA instructed the applicant to compile information regarding the utilization of anticoagulant and antiplatelet therapies and the incidence and nature of hemorrhagic complications in clinical studies and to sufficiently provide users with such information through training programs, the instructions for use, and other materials so as to ensure that users select appropriate anticoagulant and antiplatelet therapies on an individual patient-basis. The applicant agreed. PMDA also considers that the applicant should collect information regarding the utilization of anticoagulation and antiplatelet therapies and the incidence of hemorrhagic or thrombotic adverse events through a use-results survey and take additional risk mitigation measures as necessary (Approval Condition 2).

6.B.(7) Post-marketing safety measures

6.B.(7).1) Training

The applicant plans to provide the training programs shown in Table 59 and technical support from proctors (instructors) to ensure an effective and safe introduction of the MitraClip NT System to Japan.

Table 59. Overview of training programs

Training program	Contents	Trainee
Basic training program	[redacted]	[redacted]
Patient screening program		
Catheterization laboratory simulation program		

The applicant's explanation about the appropriateness of these introduction support measures:
As in the US and Europe, company's proctors will support the introduction of the MitraClip NT System by providing training programs and attending the entire process of the procedure. A proctor system, training programs, qualification of institution's eligibility, criteria for performing the procedure without a proctor, and other supports that are similar to those in other countries will be installed in Japan. As shown in Table 60, with the proctor system, training programs, and other supports, the acute procedural success rate in the US and Europe exceeded 80% in all of the recent registries, or even 90% in STS/ACC TVT registry. In addition, the Japanese clinical study, in which the MitraClip NT System was introduced in a similar manner, showed a similar acute procedure success rate. These findings indicate that the introduction and administration of the MitraClip NT System are appropriate.

Table 60. Acute procedural success rate in each study in foreign registries

Registry	Acute procedural success	Study period
STS/ACC TVT (US)[22]	92%	Registered [redacted]
SENTINEL (EU)[23]	95%	Registered [redacted]
ACCESS (EU)[24]	91%	Registered [redacted]
TRAMI (DE)[25]	95%	Registered [redacted]
MitraSwiss (CH)[26]	85%	Registered [redacted]
France (FR)[27]	88%	Registered [redacted]
GRASP (IT)[28]	100%	Registered [redacted]
MARS (Asia)[29]	94%	Registered [redacted]
Japanese clinical study	87%[a]	Registered: [redacted] to [redacted]

Gorav Ailawadi, Updated MitraClip Outcomes from the STS TVT Registry, TCT 2016

[a] In the Japanese clinical study, the severity of MR was assessed by ECL.

PMDA's view:

The Japanese clinical study has shown a procedural success rate as good as that in the US and Europe, in which there is plenty of experience with the use of the MitraClip NT System. Instructions by proctors (instructors) who have a thorough knowledge about the MitraClip NT procedure are expected to further improve the procedure. The technical support measures planned by the applicant are appropriate. Although the MitraClip NT System reduces MR in a less invasive manner than surgery, it is unavoidably associated with a certain risk of procedural failure and related complications. As a premise of using the MitraClip NT System, patients must be adequately treated with optimal medical therapy because functional MR may respond to medial therapy. To maximize the risk-benefit balance of the MitraClip NT System in the target patient population, it is crucial for physicians to fully understand the characteristics of the MitraClip NT procedure, including the above issues, and then to decide whether to use it after considering continuation of conventional medical therapies and surgery. Since complications related to the MitraClip NT System or its procedure need to be treated appropriately, the MitraClip NT System should be used by physicians who have sufficient experience and capability of performing medical and surgical treatments of severe cardiac failure in patients with severe MR at medical institutions well-equipped to treat such patients. This should be included as an approval condition (Approval Condition 1).

The proper use of the MitraClip NT System, as well as the qualifications of treating physicians and medical institutions plan to be established mainly by the Japanese Circulation Society, which submitted a written request for the introduction of the MitraClip NT System as a high-need medical device.

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

Table 61 shows a summary of the planned use-results survey of MitraClip NT System. The applicant plans to conduct a use-results survey involving all patients (up to 500) for 6 years (preparation for marketing, 6 months; patient registration, 2 years; follow-up, 3 years; analysis, 6 months).

Table 61. Summary of the use-results survey

Objectives	To understand the incidence of device malfunctions and their status in order to ensure the safety, etc., as well as to collect safety and efficacy evaluation data for the use-results assessment.
Population	Patients with severe MR who can be candidates for the MitraClip NT procedure
Target sample size	All patients (up to 500)
Survey period	6 years (preparation for marketing, 6 months; patient registration, 2 years; follow-up, 3 years; analysis, 6 months)
Main survey items	Incidence of single leaflet device attachment and acute procedural success
Other survey items	The same as those for clinical studies of interventions for MR in general (e.g., MR severity, NYHA Functional Class, left ventricular function and anatomy, the rate of hospitalization, use of cardiovascular drugs, adverse events, and device dysfunction)

The survey will include all patients because (i) the MitraClip NT procedure is highly innovative and (ii) procedural outcome (success or failure) have a significant impact on the treatment outcome. The maximum sample size of 500 was selected so that the incidence of single leaflet device attachment, a risk specific to the MitraClip NT procedure, can be determined with a certain probability.

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

The applicant's explanation:
The safety data collected at 5-year follow-up in the Integrated High Risk Cohort were analyzed. Cardiac and vascular adverse events were most common at 30-day follow-up. The incidence of adverse events in each category was low and stable between 30-day and 5-year follow-up visits. Subjects with degenerative MR and subjects with functional MR had a similar incidence of adverse events.

On the basis of these findings, the duration of the use-results survey of 3 years is appropriate for the MitraClip NT System.

PMDA generally agreed with and accepted the applicant's explanations because the applicant plans to report the long-term outcome of the MitraClip NT procedure based on the analysis of the submitted clinical study results regarding the long-term outcome [see Section "6.(B).(4) Specific risks of MitraClip NT System"] and because the Japanese clinical study identified no risks specific to Japanese patients.

8. Description on Package Inserts Specified in Paragraph 1 of Article 63-2 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

8.A Summary of the data submitted

The applicant submitted instructions for use (draft) in accordance with the "Marketing Applications for 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 comments raised in the Expert Discussion, PMDA concluded that there were no particular problems with the information included in the instructions for use at that point provided that the necessary precautions are given, as described in "6.B Outline of the review conducted by PMDA."

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

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

IV. Overall Evaluation

The MitraClip NT System was developed for the transcatheter treatment of MR. PMDA's review of the application for the MitraClip NT System focused on (1) its efficacy and safety and (2) post-marketing safety measures. Based on comments raised in the Expert Discussion, PMDA reached the following conclusions:

(1) Efficacy and safety of MitraClip NT System

The results of the foreign clinical studies showed that the interventional treatment with the MitraClip NT System improved MR severity, NYHA Class, and the rate of hospitalization in high-surgical-risk patients with symptomatic degenerative or functional MR who had a relatively well-maintained cardiac function. The risk associated with the interventional treatment with the MitraClip NT System was assessed by comparing the data with this treatment and the propensity-score-matched data from the database of medical therapy in the US. The comparison suggested that the interventional treatment with the MitraClip NT System did not increase the mortality at 12-month follow-up. The Japanese clinical study showed similar results. Patients with symptomatic severe MR have a poor prognosis despite adequate treatment of the primary disease, including medical therapy. In addition, there is no effective treatment available for high-surgical-risk patients. For these reasons, the benefits of MitraClip NT procedure outweigh its risks as shown by the results of the foreign and Japanese clinical studies. The MitraClip NT System can be a new treatment option for patients with symptomatic severe MR who are at high risk for surgery.

(2) Post-marketing safety measures

Although the MitraClip NT System reduces MR in a minimally invasive manner, it is unavoidably associated with a certain risk of procedural failure and its related complications. To maximize the risk-benefit balance of the MitraClip NT System in the target patient population, it is crucial for physicians to acquire necessary techniques through training programs, the proctor system, and by other means, to fully understand the characteristics of the MitraClip NT procedure, and then to decide whether to use it after considering conventional medical therapies and surgery. Since complications related to the MitraClip NT System or to the procedure need to be treated appropriately, the MitraClip NT System should be used by physicians who have sufficient experience and capability of performing medical and surgical treatments of severe cardiac failure in patients with severe MR at medical institutions well-equipped to treat such patients (Approval Condition 1). The MitraClip NT System will be the first medical device approved for the transcatheter treatment of MR in Japan. Post-marketing information regarding the MitraClip NT procedure, including procedural success rate

and the incidences of adverse events, in Japan should be collected through a use-results survey to take additional risk mitigation measures as necessary (Approval Condition 2). There is only limited knowledge about the long-term outcome of the MitraClip NT procedure in and outside Japan. It is, therefore, appropriate to follow up patients for 3 years and conduct the use-results survey for 6 years (preparation for marketing, 6 months; patient registration, 2 years; follow-up, 3 years; analysis, 6 months). Moreover, the applicant should submit annual reports from the submitted clinical studies to review the long-term outcome of the MitraClip NT procedure. This should be added as an approval condition (Approval Condition 3).

As a result of its review, PMDA has concluded that the MitraClip NT System may be approved for the following intended use.

Intended Use

Treatment of mitral regurgitation in patients with symptomatic severe mitral regurgitation (MR severity 3+ or 4+) with a left ventricular ejection fraction of ≥30% who are at high risk for open-heart surgery, except for patients who:

- Have functional mitral regurgitation that has not been adequately treated with optimal medical therapy recommended by Japanese guidelines,
- are experiencing acute worsening,
- have dependence on inotropic drugs (catecholamine), or
- are using assisted circulation.

Approval Conditions

1. The applicant is required to take necessary measures, such as dissemination the guideline for proper use developed in cooperation with related academic societies and provision of training programs, to ensure that physicians with adequate knowledge and experience in treating symptomatic severe mitral regurgitation in high-surgical-risk patients acquire sufficient skills for using the product and knowledge about procedure-related complications, and that the product is used in accordance with the intended use and directions for use of the product at medical institutions appropriately equipped to treat the disease.
2. The applicant is required to conduct a post-marketing use-results survey involving all patients treated with the product until data from a specified number of patients have been gathered, to submit annual reports on the results of analyses of long-term outcomes to the Pharmaceuticals and Medical Devices Agency (PMDA), and to take appropriate measures as necessary.
3. The applicant is required to submit annual reports on the results of analyses of long-term outcome data from participants in the clinical studies for regulatory submission to PMDA 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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