August 4, 2021
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 07, Organ Function Replacement Device
Term Name	Transcatheter porcine pericardial valve
Brand Name	Harmony Transcatheter Pulmonary Valve Replacement System
Applicant	Medtronic Japan Co., Ltd.
Date of Application	November 27, 2020 (Application for marketing approval)

Results of Deliberation

In its meeting held on August 4, 2021, 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 should be designated as a medical device subject to a use-results survey, and should be approved. The product should be classified as a biological product.

The use-results survey period should be 7 years and 6 months.

The intended use of the product should be as follows:

The Harmony Transcatheter Pulmonary Valve Replacement System is used in patients with severe pulmonary regurgitation who previously underwent surgical repair or transcatheter intervention (balloon valvuloplasty) for the right ventricular outflow tract and clinically need pulmonary valve replacement. These patients are eligible only if they are at high risk of surgery and their optimal treatment is treatment with the Harmony Transcatheter Pulmonary Valve Replacement System. Patients who have a right ventricle-to-pulmonary artery conduit or a prosthetic valve are not eligible for treatment with the Harmony Transcatheter Pulmonary Valve Replacement System.

Review Report

July 8, 2021

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	Transcatheter porcine pericardial valve
Brand Name	Harmony Transcatheter Pulmonary Valve Replacement System
Applicant	Medtronic Japan Co., Ltd.
Date of Application	November 27, 2020
Items Warranting Special Mention	Orphan Medical Device
Reviewing Office	Office of Medical Devices I

Review Results

July 8, 2021

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Transcatheter porcine pericardial valve
Brand Name	Harmony Transcatheter Pulmonary Valve Replacement System
Applicant	Medtronic Japan Co., Ltd.
Date of Application	November 27, 2020

Results of Review

The Harmony Transcatheter Pulmonary Valve Replacement System (hereinafter referred to as the "Harmony TPV System") is a transcatheter porcine pericardial valve used in patients with severe pulmonary regurgitation who previously underwent surgical repair or transcatheter intervention (balloon valvuloplasty) for the right ventricular outflow tract and clinically need pulmonary valve replacement. The Harmony TPV System consists of a transcatheter pulmonary valve, a delivery catheter, and a loading system.

The applicant submitted non-clinical data supporting the physicochemical properties, biological safety, stability, durability, and performance. The data had no particular problems.

The applicant submitted analysis results of pooled data from 2 clinical studies of the Harmony TPV System: the Native EFS study, a feasibility study conducted in the US and Canada; and the Harmony TPV study, a study conducted in Japan, the US, and Canada.

The analysis of the pooled data showed that "the percentage of subjects with acceptable hemodynamic function at 6 months" (the primary efficacy endpoint) was 89.2% (58 of 65 evaluable subjects), with the lower limit of the 95% confidence interval (CI) of 79.1%. Thus the performance target of 75% was met. The primary safety endpoint was "freedom from procedure- or device-related mortality at 30 days post-implant," and there were no deaths at 30 days post-implant (0 of 71 subjects). The long-term data for the Harmony TPV System include the following: in the Native EFS study, 17 subjects completed the 5-year follow-up period and finished the study; in the Harmony TPV study, 11 subjects completed the 2-year follow-up period and 2 subjects completed the 3-year follow-up period. The Kaplan-Meier estimate for freedom from device failure was 82.8% at 1 year post-implant and 69.4% at 5 years post-implant.

According to the submitted clinical evaluation data, the Harmony TPV System was shown to have a certain level of efficacy and safety as a prosthetic valve in the relatively early phases after

implantation, but some patients had to undergo reintervention or experienced valve dysfunction. The existing surgical procedures have shown favorable outcomes, including long-term outcomes, in Japan, and reoperation after Harmony TPV implantation is associated with considerably high risk. Therefore, at present, Harmony TPV System should be clinically positioned as a treatment option for patients who are ineligible for surgery and have no other effective treatment options. The Harmony TPV System can reduce regurgitation of the pulmonary valve less invasively than surgery, but there remains the risk of unsuccessful procedure and associated complications. For this reason, to keep a favorable risk-benefit balance of the Harmony TPV System in the intended patient population, the user should properly determine whether treatment with the Harmony TPV System is optimal for the patient, after (a) mastering the techniques required for placement of the Harmony TPV through training or other means, (b) fully understanding the characteristics of treatment with the Harmony TPV System, and (c) considering conventional treatment options (i.e., surgical procedures). Furthermore, appropriate actions should be taken in case of complications associated with the Harmony TPV System or with placement technique. Therefore, PMDA has concluded that treatment with the Harmony TPV System should be performed by physicians with sufficient experience in medical and surgical treatments for patients with congenital heart disease who can provide suitable care at medical institutions with such experience and that can provide such care.

There is limited clinical experience in transcatheter treatment of pulmonary regurgitation in Japan. In addition, long-term data on the Harmony TPV System are insufficient in Japan and other countries. PMDA concluded that the applicant should report data from the submitted clinical studies over a long period of time, examine the clinical data on the Harmony TPV System (e.g., the procedural success rate and adverse events) from the use-results survey to be conducted based on the post-marketing safety actions described above, and should take additional risk minimization actions as necessary.

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

Intended Use

The Harmony Transcatheter Pulmonary Valve Replacement System is used in patients with severe pulmonary regurgitation who previously underwent surgical repair or transcatheter intervention (balloon valvuloplasty) for the right ventricular outflow tract and clinically need pulmonary valve replacement. However, such patients are eligible only if they cannot undergo surgery and the Harmony Transcatheter Pulmonary Valve Replacement System is considered to

offer the optimal treatment for them. Patients who have a right ventricle-to-pulmonary artery conduit or a prosthetic valve are not eligible for treatment with the Harmony Transcatheter Pulmonary Valve Replacement System.

Approval Conditions

1. The applicant is required to take necessary actions in cooperation with the relevant academic societies to ensure that the Harmony Transcatheter Pulmonary Valve Replacement System is used only by medical teams with sufficient knowledge and experience in the treatment of congenital heart disease at medical institutions capable of providing treatment for complications associated with treatment with the Harmony Transcatheter Pulmonary Valve Replacement System.
2. The applicant is required to take necessary actions in cooperation with the relevant academic societies to ensure that the Harmony Transcatheter Pulmonary Valve Replacement System is used, in compliance with the approved indication, by physicians of a medical team satisfying the Approval Condition 1, who have mastered techniques required for manipulating the Harmony Transcatheter Pulmonary Valve Replacement System, have fully learned complications associated with the Harmony TPV procedure, and have acquired other necessary knowledge, by receiving a training program etc.
3. The applicant is required to take necessary actions to ensure that the Harmony Transcatheter Pulmonary Valve Replacement System is used only for eligible patients, in cooperation with the relevant academic societies.
4. The applicant is required to conduct a use-results survey covering all patients treated with the Harmony Transcatheter Pulmonary Valve Replacement System after the market launch, to provide PMDA with the analysis results of long-term outcomes, and to take appropriate actions as necessary.
5. The applicant is required to provide PMDA with the analysis results of the long-term outcomes in participants of the clinical studies submitted for the present application, and to take appropriate actions as necessary.

Review Report

July 8, 2021

Product for Review

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Transcatheter porcine pericardial valve
Brand Name	Harmony Transcatheter Pulmonary Valve Replacement System
Applicant	Medtronic Japan Co., Ltd.
Date of Application	November 27, 2020
Proposed Intended Use	The Harmony Transcatheter Pulmonary Valve Replacement System is used in patients with severe pulmonary regurgitation who previously underwent surgical repair (patch repair) or transcatheter intervention (balloon valvuloplasty) for the right ventricular outflow tract and clinically need pulmonary valve replacement. Patients who have a right ventricle-to-pulmonary artery (RV-PA) conduit or a prosthetic valve are not eligible for treatment with the Harmony Transcatheter Pulmonary Valve Replacement System.
Items Warranting Special Mention	Orphan Medical Device

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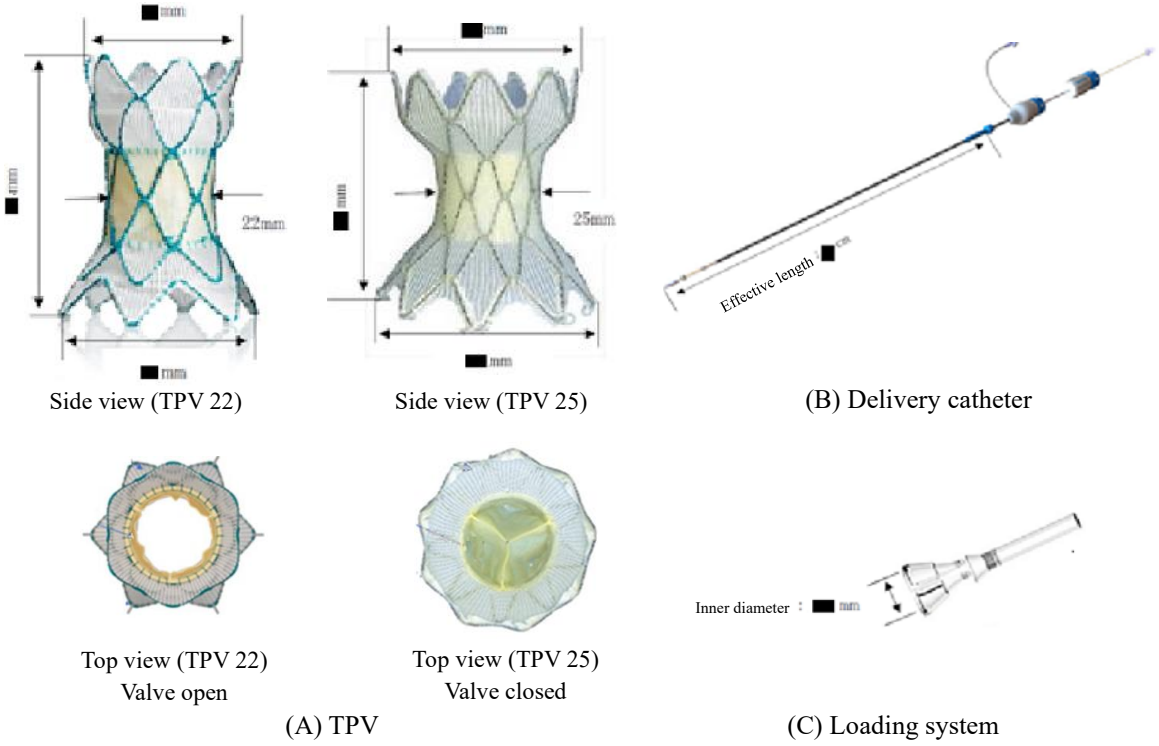
List of Abbreviations

ASTM	American Society for Testing and Materials
BBB	Borate Buffered Biocide
CEC	Clinical Events Committee
CT	Computed Tomography
DORV	Double-Outlet Right Ventricle
EFS	Early Feasibility Study
ePTFE	Expanded Polytetrafluoroethylene
ICD	Implantable Cardioverter Defibrillator
ISO	International Organization for Standardization
LVEDV	Left Ventricular End-Diastolic Volume
MRI	Magnetic Resonance Imaging
PA	Pulmonary Artery
PRF	Pulmonary Regurgitant Fraction
QOL	Quality of Life
RV	Right Ventricle
RVEDV	Right Ventricular End-Diastolic Volume
RVEDVi	Right Ventricular End-Diastolic Volume index
RVEF	Right Ventricular Ejection Fraction
RVESV	Right Ventricular End-Systolic Volume
SF-36	Short Form 36-item Health Survey
TPV	Transcatheter Pulmonary Valve

I. Product Overview

"The Harmony Transcatheter Pulmonary Valve Replacement System" (hereinafter referred to as the "Harmony TPV System") is a transcatheter porcine pericardial valve used in patients with severe pulmonary regurgitation who previously underwent surgical repair or transcatheter intervention (balloon valvuloplasty) for the right ventricular outflow tract and clinically need pulmonary valve replacement. The Harmony TPV System consists of a transcatheter pulmonary valve (TPV) and a delivery system to place the TPV (a delivery catheter and a loading system) (Figure 1). The TPV, available in 2 sizes (TPV 22 and TPV 25), is composed of a porcine pericardial tissue valve sutured to a self-expanding stent-graft made of nickel-titanium alloy and a polyester fabric covering. The TPV is loaded onto a delivery catheter by the loading system and delivered percutaneously to the right ventricular outflow tract through vessels (Figure 2).



Side view (TPV 22) Side view (TPV 25) (B) Delivery catheter

Top view (TPV 22) Valve open Top view (TPV 25) Valve closed

(A) TPV (C) Loading system

Figure 1. Appearance of the components of Harmony TPV System

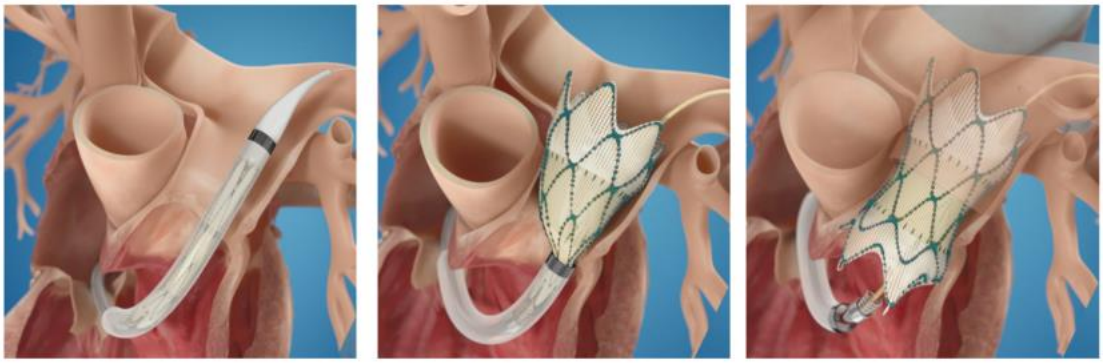


Figure 2. Implantation of the Harmony TPV System in the pulmonary valve position

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 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 Harmony TPV System declared that they did not fall under Item 5 of the Rules for Convening Expert Discussions etc. issued by the 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

Abnormalities of the right ventricular outflow tract and the pulmonary valve are most commonly present in patients with congenital heart disease such as tetralogy of Fallot and pulmonary stenosis, and generally require surgery or other intervention early after birth (during infancy and early childhood). The right ventricular outflow tract and/or pulmonary valve repaired early in life cease to function efficiently as the child grows, increasing the incidence of pulmonary valve incompetence. While the effect of pulmonary valve incompetence (pulmonary regurgitation) varies among patients, long-term follow-up studies have clarified its adverse effects on right ventricle and left ventricle functions. More specifically, pulmonary valve incompetence results in chronic volume overload to the right ventricle, leading to ventricular dilation, systolic dysfunction or diastolic dysfunction. The prolonged volume overload of the right ventricle causes reduced exercise tolerance, arrhythmia, and increased risk for sudden death. In many cases, patients undergo reoperation during adolescence. Recovery of pulmonary valve function at an appropriate time will improve right ventricle function, reduce the incidence of arrhythmia, and improve exercise tolerability.

Currently available therapies to restore pulmonary valve function include implantation of an extracardiac conduit connecting the right ventricle to the main pulmonary artery (hereinafter referred to as “right ventricle-to-pulmonary artery conduit”), surgical bioprosthetic valve replacement, and corrective approach to preserve valve function. While these surgical procedures can reduce mortality, there remains the risk associated with the use of cardiopulmonary bypass and the risk of infection, haemorrhage, and exacerbated ventricular dysfunction. Furthermore, there have been reports[1,2] that the risk of serious procedure-related complications such as death and heart injury increases in patients who undergo multiple reoperations. The cumulative risk of specific complications (in-hospital death, condition requiring mechanical circulatory support, and arrhythmia) increases after every operation.[3]

Transcatheter pulmonary valve implantation is a technique developed for patients whose right ventricle-to-pulmonary artery conduit or bioprosthetic valve does not function properly. Medtronic Melody™ TPV (hereinafter referred to as “Melody TPV”), a transcatheter valve replacement system, was approved in the US in 2015 and is indicated for patients requiring clinical intervention who have a dysfunctional bioprosthetic valve or right ventricle-to-pulmonary artery conduit with moderate or severe regurgitation or right ventricular outflow tract gradient of ≥35 mmHg. (Melody TPV has not been approved in Japan.) Data from clinical experience with the Melody TPV showed that the product could be implanted safely in patients and improved objective indicators of cardiac function in the acute phase, medium-term (3-5 years), and long-term (7-10 years). However, only approximately 25% of patients with right ventricular outflow tract anomalies have undergone implantation of a right ventricle-to-pulmonary artery conduit or bioprosthetic valve. The remaining approximately 75% have not received the conduit or bioprosthetic valve, but instead have undergone surgical procedures such as patch repair and balloon valvuloplasty (the right ventricular outflow tract is preserved in these procedures); however, pulmonary valve incompetence occurring late after the procedure is a clinically challenging issue in these patients. Treating these patients by transcatheter pulmonary valve replacement, as with Melody TPV, is less invasive and is likely to reduce the number of surgeries required in the lifetime of the patient.

The Harmony TPV System was developed for patients with congenital heart disease who do not have a right ventricle-to-pulmonary artery conduit in the right ventricular outflow tract and clinically need pulmonary valve replacement. In 20[redacted], a feasibility study (Native EFS study) started in the US and Canada. After further improvements to the device, the Harmony TPV study started in 20[redacted] in the US and Canada; Japan participated in the study from 20[redacted]. During the process of development, various changes were made to the Harmony TPV System: addition of

another product size, change of raw materials and morphology, and modifications to enhance operability. Table 1 summarizes the history of development of the Harmony TPV System.

Table 1. History of development of the Harmony TPV System

TPV 22

Model	Major changes from the previous model	Clinical study (number of patients who received the device)
TPV 22 earlier model	—	Native EFS (N = 20)
cTPV 22 (predecessor model)	• Change [redacted].	Harmony TPV (N = 21)
Proposed device	• Change [redacted]. • Change [redacted] to prevent stent wire fracture.	—

TPV 25

Model	Major changes from the previous model	Clinical study (number of patients who received the device)
cTPV 25 (predecessor model)	—	Harmony TPV (N = 19)
Proposed device (mTPV 25)	• [redacted] to prevent maldeployment of cTPV 25, which had occurred in the clinical study. In addition, [redacted]. • Change [redacted].	Harmony TPV (N = 10)

Delivery system

Model	Major change from the previous model	Clinical study
Clinical delivery catheter system	—	Native EFS and Harmony TPV
Proposed device	• Change [redacted]. • Change [redacted]. • Change [redacted].	—

The Harmony TPV System was designated as an orphan medical device (PSEHB/MDED Notification No.1217-1, dated December 17, 2020, by the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare).

1.A.(2) Use in foreign countries

Table 2 shows the approval statuses of the Harmony TPV System in other countries. The Harmony TPV System has been granted approval only in the US. As of June 7, 2021, [redacted] units of TPV 22, [redacted] units of TPV 25, and [redacted] units of the delivery catheter system have been sold.

Table 2. Approval status in other countries

Country	Brand name	Approval date	Intended use or indication
US	Harmony Transcatheter Pulmonary Valve (TPV) System	March 26, 2021	The Harmony Transcatheter Pulmonary Valve (TPV) System is indicated for use in the management of pediatric and adult patients with severe pulmonary regurgitation (i.e., severe pulmonary regurgitation as determined by echocardiography and/or pulmonary regurgitant fraction ≥30% as determined by cardiac magnetic resonance imaging) who have a native or surgically-repaired right ventricular outflow tract and are clinically indicated for surgical pulmonary valve replacement.

1.A.(3) Malfunctions and incidence of adverse events outside Japan

No malfunctions have occurred as of June 7, 2021.

2. Design and Development

2.(1) Performance and safety specifications

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

The proposed performance specifications for the TPV of the Harmony TPV System included pulsatile flow testing, accelerated durability testing, total regurgitant volume ([redacted]), radiopacity, corrosion resistance of the frame, MRI compatibility, post-deployment dimensions, and the testing of chronic outward force. The proposed performance specifications for the delivery catheter included bond strength testing, hemostasis testing, corrosion resistance testing, and radiopacity. The proposed performance specifications for the entire system included guidewire compatibility, and loading/delivery/deployment of the TPV. The proposed safety specifications included biological safety, sterility, testing of bacterial endotoxins, and ethylene oxide sterilization residuals.

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

The acceptance criterion of the total regurgitant fraction was defined as ≤[redacted]% in the pulsatile flow testing of the TPV. PMDA asked the applicant to explain the rationale for the criterion. The acceptance criteria of the chronic outward force included only the lower limit. PMDA asked the applicant to consider specifying the upper limit of the chronic outward force to define the expanding force of the Harmony TPV System taking into account the impact on pulmonary artery tissues.

The applicant's explanation:

The acceptance criterion of the total regurgitant fraction in the pulsatile flow testing is appropriate for the following reasons:

(a) [redacted] pulmonary regurgitation is defined as regurgitation [redacted] of <[redacted]%.[4]

(b) ISO 5840-3:2013 requires that the upper limit of the total regurgitant fraction be [redacted]% for the performance [redacted]. Applying the requirements for [redacted] to the pulmonary artery is a conservative approach because the pulmonary artery is less likely to be affected by regurgitation.

The applicant proposes the upper limit of <[redacted] N for the testing of chronic outward force. This upper limit is based on the comparison of the force trends identified in a study of oversized stent implantation in the ovine model. The report of the study suggested that a chronic outward force of >[redacted] N may induce damage to [redacted] and a chronic outward force of >[redacted] N damage to [redacted].[5] According to [redacted] shown in the report, the upper limit of chronic outward force in the ovine model is below the upper limit that induces damage to [redacted]. Therefore, defining the upper limit of chronic outward force of the Harmony TPV based on the results of the ovine [redacted] study is a conservative and reasonable approach.

PMDA's view:
The applicant's explanation and actions are reasonable. PMDA examined the appropriateness of the tests and acceptance criteria specified in the proposed performance and safety specifications, and found no particular problems.

2.(2) Physicochemical properties

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

2.(2).A.1) Studies of TPV

To support the physicochemical properties of the TPV, the applicant submitted data from the following tests that used the proposed devices, the earlier model, or the predecessor models (Table 1): hydrodynamic testing, accelerated durability testing, total regurgitant flow testing ([redacted]), chronic outward force testing, valve migration resistance testing, structural integrity testing, post-deployment dimensions, post-conditioning inspection, corrosion testing, MRI compatibility testing (evaluation of heating, magnetic displacement force, torque, and image artifacts during the use of 1.5- or 3-Tesla MR system), tissue uniaxial tensile strength testing, dynamic failure mode testing, particle image velocimetry, dynamic regurgitation testing, and TPV foreshortening testing.

The following testing was performed using TPV 22 and mTPV 25 (proposed devices) and the results showed no problems: Hydrodynamic testing, total regurgitant flow testing ([redacted]), chronic outward force testing, post-deployment dimensions, post-conditioning inspection, particle image velocimetry, dynamic regurgitation testing, and TPV foreshortening

testing. The valve migration resistance was comprehensively evaluated based on data from migration testing of TPV 22 (proposed device), chronic outward force testing of TPV 22 and mTPV 25 (proposed devices), and other clinical studies. The evaluation results demonstrated that the proposed devices had acceptable migration resistance.

Accelerated durability testing was performed using cTPV 22 and cTPV 25 (predecessor models), and the results demonstrated that they met the acceptance criteria. The applicant explained the following rationale for using the predecessor models to evaluate the proposed devices:

Although cTPV 22 and TPV 22 (proposed device) [redacted], [redacted].

Dynamic failure mode testing was performed by using the same specimens used in the accelerated durability testing to evaluate the potential failure mode associated with deterioration of valves under ultra-high pressure conditions, and identified failure modes including leaflets becoming fragile, suture breakage, and wire fracture. For the testing of structural integrity, (a) a finite element analysis was conducted to evaluate the device characteristics such as stent strut distortion and fatigue; and (b) fatigue testing was performed using stent strut sections of the proposed devices, and the results showed no fractures.

Corrosion testing was performed using cTPV 25 [redacted], and the results showed no problems. MRI compatibility testing was performed using the TPV 22 earlier model and cTPV 25, and the results showed that they were MRI conditional. Accordingly, cautionary statements regarding the conditions required for using MRI were included in the instructions for use in an appropriate manner. Tissue uniaxial tensile strength testing was performed using the same porcine pericardial tissue to be used in the proposed devices, and the results showed no problems.

2.(2).A.2) Delivery catheter system testing

To support the physicochemical properties of the delivery catheter system, the applicant conducted the following tests using the proposed device: visual inspection, dimensional inspection, loading/deployment testing, hemostasis testing, bond strength testing, corrosion resistance testing, and ergonomics testing. The results submitted by the applicant showed no problems.

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

PMDA reviewed the data on the physicochemical properties and concluded that there were no particular problems.

2.(3) Biological safety

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

The applicant submitted the results of a biological safety study of the Harmony TPV 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 ISO 10993-1.

To support the biological safety of the TPV, the following studies were conducted using cTPV 22 (predecessor model) (Table 1): cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, genotoxicity (bacterial reverse mutation assay, chromosomal aberration assay, and micronucleus assay), pyrogen, implantation (4-week and 13-week intramuscular implantation, 13-week systemic toxicity after subcutaneous implantation), and hemocompatibility (ASTM hemolysis, C3a complement activation, SC5b-9 complement activation, and partial thromboplastin time). The submitted results of these studies showed no problems. The applicant explained that cTPV 22 and TPV 22 (proposed device) [redacted] there were no safety problems. The applicant also explained that cTPV 22 and mTPV 25 (proposed device) [redacted] the fabric covering used in mTPV 25 (proposed device) is identical to the raw material used in implantable devices such as the Medtronic's approved device "[redacted]" (Approval No. [redacted]) and therefore there were no safety problems.

To support the biological safety of the delivery catheter system, the following studies were conducted using the proposed device: cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, pyrogen, and hemocompatibility (ASTM hemolysis, SC5b-9 complement activation assay, *in vivo* anti-thrombogenicity), and the submitted study results showed no problems.

The Harmony TPV is sterilized and packaged in a [redacted]% glutaraldehyde solution. Prior to implantation, the TPV must be washed with sterile physiological saline. To demonstrate the effectiveness of washing, the applicant conducted a glutaraldehyde residual test of TPV after washing, and submitted the results.

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

PMDA reviewed the data on biological safety, and concluded that there were no particular problems.

2.(4) Stability and durability

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

To support the stability of the TPV, the applicant conducted a stability study (hydrodynamic properties) using samples of cTPV 22 (predecessor model) and mTPV 25 (proposed device) (Table 1) that had been stored for 1 year in real time. The submitted results showed that all samples that had been stored under real time conditions met the acceptance criteria. The applicant explained that the use of cTPV 22 for evaluating TPV 22 (proposed device) was appropriate because this study was intended to evaluate the valves and [redacted].

The raw materials used in the proposed device are generally used in disposable medical devices. The applicant therefore submitted a self-declaration regarding the stability of the delivery catheter system in accordance with the "Handling of stability studies for determining shelf life in the application for marketing approval (certification) of medical devices" PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012.

The applicant conducted studies listed in Section "2.(2) Physicochemical properties" to evaluate durability, namely, accelerated durability testing, structural integrity testing, and dynamic failure mode testing. The submitted results showed no particular problems.

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

PMDA reviewed the data on stability and durability, and concluded that there were no particular problems.

2.(5) Performance

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

The applicant submitted the results from a chronic animal study using sheep to support the performance of the Harmony TPV System. Table 3 summarizes the study.

Table 3. Outline of chronic animal study

Device tested (number of animals)	Details of evaluation
Test device: TPV 22 earlier model* (N = 7) Control device: Hancock valved conduit (N = 3)	The test device or control device was implanted in sheep for 20 to 24 weeks (long-term). The devices were assessed for the following aspects based on the acute testing, long-term monitoring, and necropsy findings after long-term implantation. **Direct comparison between test device and control device** Thrombogenicity, hematology, valve function, paravalvular leak **Evaluation of test device only** Operability of delivery system, pathology, histology, infection, stent embolization, stent fracture, surgical explantation

* The earlier model was developed before the predecessor model. See Table 1.

The direct comparison of the test device and control device (in terms of thrombogenicity, hematology, valve function, and paravalvular leak) showed similar results between the test device and the control device.

The evaluation of the test device showed no particular problems with operability of the delivery system, pathology, histopathology, and stent embolization. However, 1 animal implanted with the test device was euthanized at 10 weeks post-implant because of rapid exacerbation of clinical symptoms. The results of necropsy indicated that the valve was infected. This animal had undergone radiography under anesthesia at 8 weeks post-implant, and based on the time of radiography and exacerbation of clinical symptoms, the valvular infection was considered due to the operation under anesthesia. The remaining 9 animals including those implanted with the control device did not show any signs of infection at necropsy. Partial fracture of stent struts were found in 4 necropsied animals implanted with the test device, but these damages did not lead to device migration, vessel perforation, stent embolization, or clear impingement of valve function. The applicant also explained that the risk of stent strut fracture was acceptable based on these test results and for the following reasons:

(a) Since stent struts are sewn onto a fabric covering, the structural integrity is maintained and thus the risk of vessel perforation is considered to be low.
(b) Since the device is endothelialized, the integrity and function of the valve are maintained.

The test device was removed by the surgeon after the animals were euthanized; this showed that the device can be removed and the outflow tract can be repaired by the standard procedure.

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

PMDA asked the applicant to explain the appropriateness of using the TPV 22 earlier model as a test device for evaluation.

The applicant's explanation:

TPV 22 is a valve in a size suitable for the morphology of the ovine model. The anatomy of the right ventricular outflow tract varies among patients with congenital heart disease, making it difficult to reproduce various human anatomies using animal models. Because TPV 22 and mTPV 25 (proposed devices) are designed in a similar way using similar materials, the results of the chronic animal study are considered to be applicable, taking into account of the results of non-clinical studies (e.g., chronic outward force, valve migration resistance, and total regurgitant flow) of TPV 22 and TPV 25. The test device that resulted in stent strut fracture was not TPV 22 (proposed device) but the TPV 22 earlier model, [redacted]. Both TPV 22 and mTPV 25 (proposed devices) [redacted], and the fatigue testing suggested their excellent fatigue strength; therefore TPV 22 and mTPV 25

(proposed devices) have a lower risk of stent strut fracture. The performance data of the proposed devices are supported by the clinical study results as well as these non-clinical study results.

PMDA's view:
PMDA understands the applicant's view that the anatomy of the right ventricular outflow tract varies greatly among eligible patients and that reproducing the various anatomies using animal models is difficult. In the chronic animal study, the TPV 22 earlier model showed similar results to those of the control device. Furthermore, the studies listed in Section "2.(2) Physicochemical properties" showed no problems in valve function, migration resistance, and other basic performance of TPV 22 and mTPV 25 (proposed devices). PMDA therefore concluded that the clinical study results, to be presented later, should also be evaluated to assess the performance of the Harmony TPV System.

Based on the above, PMDA reviewed the data on performance, and concluded that there were no particular problems.

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 Harmony TPV 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") (MHLW Ministerial Announcement No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the Harmony TPV System to the Essential Principles.

(a) The conformity of the Harmony TPV System to Article 1, which stipulates preconditions, etc. for designing medical devices (particularly requirements for users, such as the expected level of technical knowledge and experience, and the expected level of education and training for users)

PMDA's view:
As described later in Section "6.B Outline of the review conducted by PMDA," conducting the following are important for ensuring a favorable risk-benefit balance of the Harmony

TPV System: (a) select appropriate users and medical institutions that perform the procedure, (b) provide training to users, and (c) ensure compliance with the proper use standard. For this reason, PMDA decided to impose approval conditions to ensure that the applicant take necessary actions.

(b) The conformity of the Harmony TPV System to Article 2, which stipulates risk management throughout the life cycle of medical devices

PMDA's view:
As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," clinical data on the Harmony TPV System is scarce in Japanese patients. The applicant is therefore required to collect data from all patients treated with the Harmony TPV System to evaluate its safety (including durability) and efficacy, and to examine the eligibility of the patients in whom the Harmony TPV System has been used. In addition, the applicant is required to take additional risk minimization actions as necessary. Therefore, PMDA decided to impose approval conditions.

(c) The conformity of the Harmony TPV System to Article 3, which stipulates the performance and function of medical devices, and to Article 6, which stipulates the efficacy of medical devices

PMDA's view:
As described later in Section "6.B Outline of the review conducted by PMDA," based on the clinical study results of the Harmony TPV System, PMDA considers that the device can be used effectively and safely in patients who cannot undergo surgery if eligible patients are selected appropriately by physicians who are familiar with the characteristics of the device. Therefore, there are no problems with the conformity of the Harmony TPV System to Articles 3 and 6.

(d) The conformity of the Harmony TPV System to Article 4, which stipulates the durability of medical devices

PMDA's view:
As described earlier in Sections 2.(2).B, 2.(4).B, and 2.(5).B, and later in Section "6.B Outline of the review conducted by PMDA," the long-term durability of the Harmony TPV System was evaluated to a certain extent in non-clinical studies, but its long-term durability

in the clinical setting has not been established. The applicant should continue to evaluate the device after the market launch, and the PMDA decided to impose approval conditions.

(e) The conformity of the Harmony TPV System to Article 8, which stipulates prevention of the microbial contamination of medical devices made from animal tissues

PMDA's view:
As described later in Section "5.(B) Outline of the review conducted by PMDA," the applicant explained the status of conformity of the porcine pericardium, a raw material of TPV, to the provisions set out in Subsection "2. Standards for Animal Cells and Tissue Materials," Section "4. General Rules for Animal Derived Materials," of the Standards for Biological Raw Materials (Public Notice No.210 of 2003 issued by the Ministry of Health, Labour and Welfare). Based on the above, the safety of the porcine pericardium, a raw material of TPV, is assured as a material of animal origin.

(f) The conformity of the Harmony TPV System to Article 9, which stipulates issues regarding the environment in which medical devices are used in combination with other medical devices

PMDA's view:
As described earlier in Section "2.(2).B Outline of the review conducted by PMDA," the Harmony TPV System was demonstrated to be MRI conditional, and the instructions for use include appropriate cautionary statements regarding the scan conditions required for MRI use. Therefore, there are no problems with the conformity of the Harmony TPV System to Article 9.

(g) The conformity of the Harmony TPV System to Article 17, which stipulates requirements on the provision of information to users through instructions for use or other materials

PMDA's view:
As described later in Section "6.B Outline of the review conducted by PMDA," in order to ensure a favorable risk-benefit balance of the Harmony TPV System, the operating physician should select eligible patients and a suitable device size after becoming fully familiar with the risks associated with the Harmony TPV System. Therefore, the applicant is required to disseminate information through the instructions for use, proper use standards, training, and by other means.

PMDA comprehensively reviewed the conformity of the Harmony TPV System to the Essential Principles, and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management, the risk management system, and its 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 comprehensively reviewed the document on risk management taking into account the discussion presented in Section "3.B Outline of the review conducted by PMDA" and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on inspections implemented during the manufacturing process of the Harmony TPV System and the sterilization method (sterilization validation, bacterial endotoxin testing, ethylene oxide sterilization residuals, and [redacted]).

The applicant explained the status of conformity of the porcine pericardium, the raw material of TPV, to the provisions set out in Subsection 2. "Standards for Animal Cells and Tissue Materials," Section 4. "General Rules for Animal Derived Materials," of the Standards for Biological Raw Materials" (Public Notice No.210 of 2003 issued by Ministry of Health, Labour and Welfare). The Harmony TPV System's process conditions for porcine pericardium and virus inactivation are the same as those of the approved device "[redacted]" (Approval No. [redacted]). The applicant therefore submitted no study data on virus inactivation.

5.B Outline of the review conducted by PMDA

PMDA reviewed the data on the manufacturing process of the Harmony TPV 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 from 2 prospective, multicenter, single-arm studies to support clinical evaluation of the Harmony TPV System: the Native EFS study (feasibility study) and the Harmony TPV study (pivotal study).

The Native EFS study is a feasibility study conducted in 3 study centers in the US and Canada. A total of 20 subjects were implanted with the TPV 22 earlier model (developed before the predecessor model. See Table 1). The Native EFS study achieved the primary endpoint. Then the Harmony TPV study was started, which was designed to implant the cTPV 22 (predecessor model) (Table 1) in a maximum of 40 patients at 15 study centers in the US, Canada, and Japan. After the start of the Harmony TPV study, the study had a high rejection rate at screening for cTPV 22. Therefore cTPV 25 (predecessor model), which is larger than cTPV 22, was developed and added as a test device (Table 1). However, there were 5 cases in which cTPV 25 was not deployed as intended, leading to interruption of cTPV 25 implantation. After the causes of maldeployment were analyzed, the design of cTPV 25 was modified, and the new mTPV 25 (proposed device) was used as a test device. Table 4 outlines the Native EFS study and Table 5 the Harmony TPV study.

When the applications for approval were filed in Japan and the US, analysis results of pooled data from the Native EFS and Harmony TPV studies were submitted for the following reasons:

(1) TPV 22 was used in both studies.
(2) Pooling data from the 2 studies enables robust evaluation based on larger data.
(3) The 2 studies had generally similar inclusion and exclusion criteria.

Table 4. Outline of Native EFS study (Study period, [redacted] 20[redacted] to [redacted] 20[redacted]): Feasibility study

Test device: TPV 22 earlier model

Item	Outline
Objective	To analyze clinical outcomes by 5-year follow-up and evaluate *in vivo* loading conditions on the device required for product development specifications.
Study design	Prospective, multicenter, single-arm study
Study population	Patients with congenital heart disease who clinically need pulmonary valve replacement
Inclusion criteria	• Patient has pulmonary regurgitation as per one or more of the following criteria: a) Severe pulmonary regurgitation as measured by continuous-wave Doppler echocardiography b) Pulmonary regurgitant fraction ≥30% as measured by cardiac MRI • Clinical indication for surgical placement of a right ventricle-to-pulmonary artery conduit or a prosthetic pulmonary valve per one or more of the following criteria: a) Patient is symptomatic secondary to pulmonary insufficiency (e.g., exercise intolerance, fluid overload) as classified by the investigator b) Patient has right ventricular end-diastolic volume index (RVEDVi) ≥150 mL/m^2 • Patient is willing to consent to participate in the study and will commit to completion of all follow-up requirements
Exclusion criteria	• Anatomy unable to accommodate a 25 Fr delivery system • Obstruction of the central veins • Clinical or biological signs of infection including active endocarditis • Indicated for intervention of stenosis of the branch pulmonary arteries at time of Harmony TPV implant • Positive pregnancy test at baseline (prior to computed tomography [CT] angiography and again prior to implant procedure) in female patients of child-bearing potential • Patients with right ventricular outflow tract obstruction lesions surgically treated with a right ventricle-to-pulmonary artery conduit implant • A major or progressive non-cardiac disease (e.g., liver failure, renal failure, cancer) that results in a life expectancy of less than 1 year • Planned implantation of the Harmony TPV in the left heart • Anatomy or morphology of the right ventricular outflow tract that is unfavorable for device anchoring • Known allergy to aspirin, heparin, or nickel • Echocardiographic evidence of intracardiac mass, thrombus, or vegetation • Pre-existing prosthetic heart valve or prosthetic ring in any position • Patient is currently enrolled in another investigational device trial or drug trial that may influence the outcome of this trial
Primary endpoint	To evaluate the pre-implant anatomy by CT and *in vivo* loading conditions pre- and post-implant
Assessment of subjects	• Clinical evaluation at pre-implant, at hospital discharge, 1 month, 3 months, 6 months, 1 year, and once a year up to 5 years • Transthoracic echocardiography at pre-implant, at hospital discharge, 1 month, 3 months, 6 months, 1 year, and once a year up to 5 years • X-ray fluoroscopy at pre-implant, 1 month, 3 months, 6 months, and 1 year • Cardiac MRI at pre-implant and 1 year • CT cardiac angiography at pre-implant and hospital discharge
Follow-up period	5 years
Sample size	Implanted in 20 patients (21 patients catheterized)
Study location (number of study centers)	US (2) and Canada (1)

Table 5. Outline of Harmony TPV study (Study period, ongoing since [redacted] 20[redacted]): Pivotal study

Test devices: (1) cTPV 22 (predecessor model)

(2) cTPV 25 (predecessor model) (interrupted)

(3) mTPV 25 (proposed device)

Item	Outline
Objective	The primary objective of this study is to demonstrate the safety and effectiveness of the Harmony TPV System as measured by freedom from procedure- or device-related mortality at 30 days and percentage of subjects with acceptable hemodynamic function at 6 months.
Study design	Prospective, multicenter, single-arm study
Study population	Patients with congenital heart disease who clinically need pulmonary valve replacement
Inclusion criteria	• Patient has pulmonary regurgitation as per one or more of the following criteria: a) Severe pulmonary regurgitation as measured by continuous-wave Doppler echocardiography b) Pulmonary regurgitant fraction ≥30% as measured by cardiac MRI • Clinical indication for surgical placement of a right ventricle-to-pulmonary artery conduit or a prosthetic pulmonary valve per one or more of the following criteria: a) Patient is symptomatic secondary to pulmonary insufficiency (e.g., exercise intolerance, fluid overload) as classified by the investigator b) Patient has right ventricular end-diastolic volume index (RVEDVi) ≥150 mL/m^2 c) Patient has right ventricular end-diastolic volume (RVEDV): left ventricular end-diastolic volume (LVEDV) ratio ≥2.0 • Patient is willing to consent to participate in the study and will commit to completion of all follow-up requirements
Exclusion criteria	• Anatomy unable to accommodate a 25 Fr delivery system • Obstruction of the central veins • Clinical or biological signs of infection including active endocarditis • Planned concomitant procedure at time of Harmony TPV implant • Positive pregnancy test at baseline (prior to CT angiography and again prior to implant procedure) in female patients of child-bearing potential • Patients with right ventricular outflow tract obstruction lesions surgically treated with a right ventricle-to-pulmonary artery conduit implant • A major or progressive non-cardiac disease (e.g., liver failure, renal failure, cancer) that results in a life expectancy of less than 1 year • Planned implantation of the Harmony TPV in the left heart • Anatomy or morphology of the right ventricular outflow tract that is unfavorable for device anchoring • Known allergy to aspirin, heparin, or nickel • Echocardiographic evidence of intracardiac mass, thrombus, or vegetation • Pre-existing prosthetic heart valve or prosthetic ring in any position
Primary endpoint	**Efficacy** Percentage of subjects with acceptable hemodynamic function at 6 months as defined by: • "Mean right ventricular outflow tract gradient as measured by continuous-wave Doppler echocardiography ≤40 mmHg" or "peak gradient as measured by cardiac catheterization ≤40 mmHg" - AND - • "Pulmonary regurgitant fraction as measured by MRI <20%" or "pulmonary regurgitation as measured by continuous-wave Doppler echocardiography is less than moderate in severity"

Item	Outline
	- AND - • No TPV reinterventions within 6 months **Safety** Freedom from procedure- or device-related mortality at 30 days post implant
Secondary endpoints	• Technical success at exit from catheterization lab/operating room • Procedural success at 30 days • Characterization of right ventricle remodeling following TPV implant as assessed via MRI • Characterization of quality of life (QOL) score over time • Device success at 5 years • TPV dysfunction at 5 years • Assessment of safety
Follow-up period	5 years* (including hemodynamic assessment as measured by echocardiography, etc.)
Sample size	cTPV 22: implanted in 21 patients (21 patients catheterized) cTPV 25: implanted in 19 patients (19 patients catheterized) mTPV 25: implanted in 10 patients (10 patients catheterized)
Study location (number of study centers)	US (9), Japan (2), and Canada (2)

* As of June 7, 2021, the follow-up period has been extended to 10 years in the US. In Japan, the period will be changed from 5 years to 10 years at the time when the study is reclassified as a post-marketing clinical study.

Figure 3 shows the disposition of subjects in the Native EFS study.

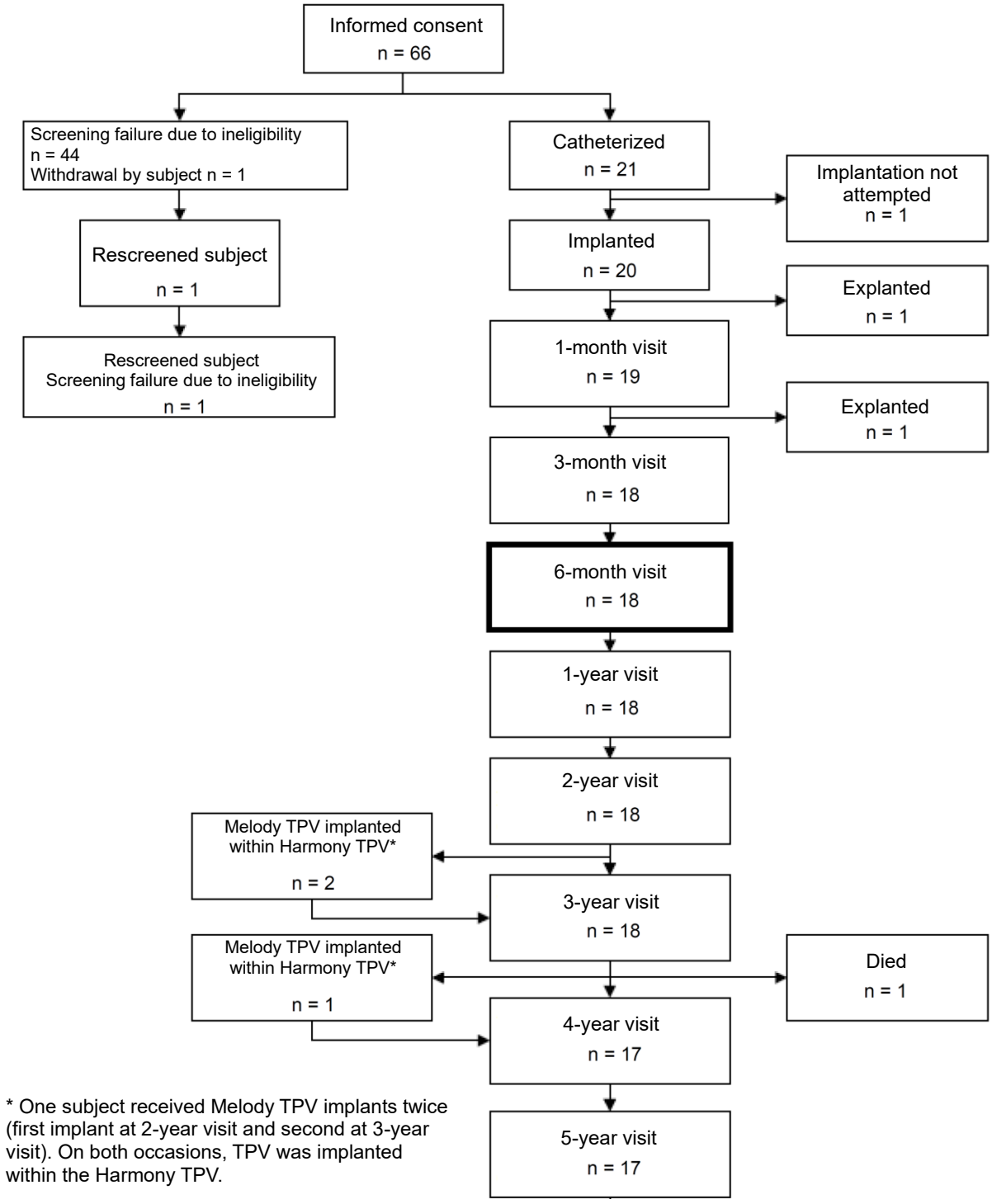


Figure 3. Disposition of subjects in the Native EFS study (feasibility study)

Figure 4 shows the disposition of subjects in the Harmony TPV study. As of [redacted], 20[redacted], 37 subjects completed the 1-year follow-up, 11 subjects the 2-year follow-up, and 2 subjects the 3-year follow-up.

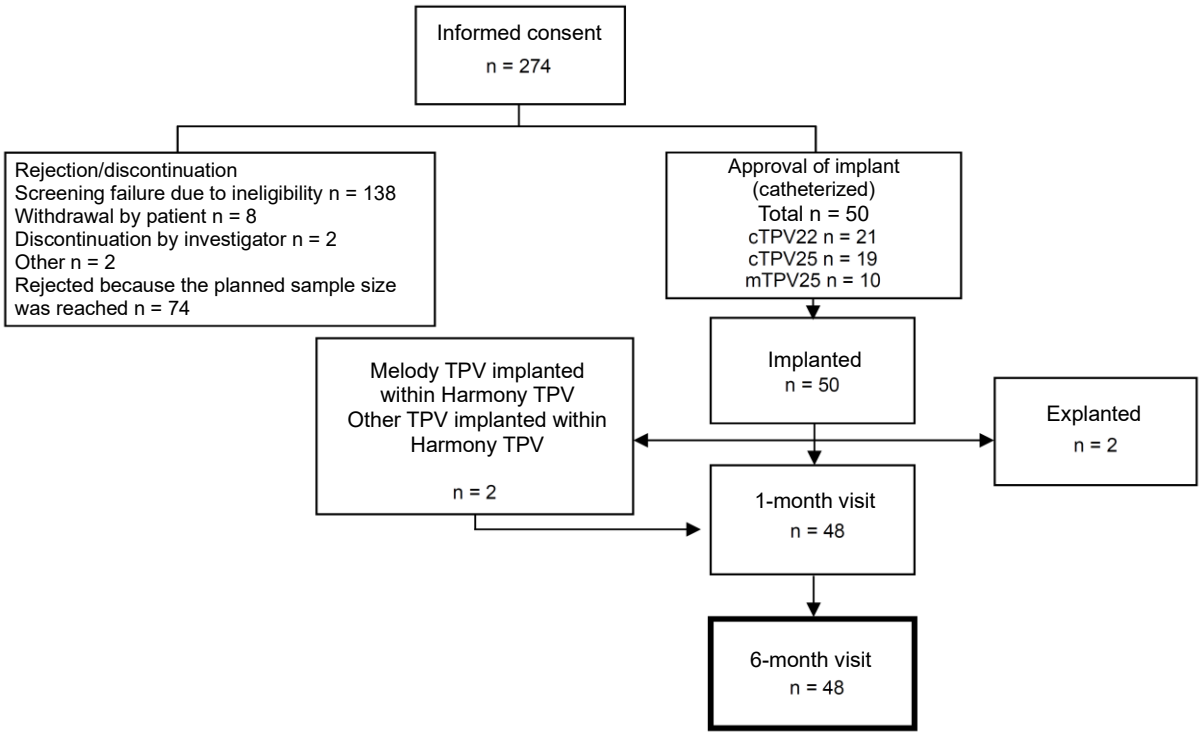


Figure 4. Disposition of subjects in the Harmony TPV study (pivotal study)

6.A.(1) Patient characteristics

Table 6 shows the baseline demographics and characteristics of patients included in the TPV Catheterized Cohort[i] in the Native EFS and Harmony TPV studies. The TPV Catheterized Cohort consisted of 42 males and 29 females with a median age (minimum, maximum) of 27 years (12 years, 59 years). Of the 71 subjects, 63 had had tetralogy of Fallot as part of their original diagnosis. The remaining subjects had other original diagnoses, with the most common diagnosis being pulmonary stenosis (3 subjects). As of the data lock date, all subjects with available echocardiography data had moderate or severe pulmonary regurgitation, with a mean right ventricular outflow tract gradient of 9.7 ± 5.3 mmHg.

All subjects underwent the procedure under general anesthesia, with venous access via either the femoral vein (67 subjects) or internal jugular vein (4 subjects). The median total procedure time (minimum, maximum) was 126 minutes (41 min, 345 min). The median total fluoroscopy time (minimum, maximum) was 34 minutes (7 min, 109 min). In 1 of the 71 subjects, catheterization

[i] TPV Catheterized Cohort consisted of all subjects who underwent catheterization for implantation of TPV.

for TPV 22 implantation was performed but TPV 22 was not implanted at the discretion of the investigator because a further evaluation revealed a high pulmonary arterial pressure.

Table 6. Baseline demographics and characteristics of patients—TPV Catheterized Cohort (N = 71)

		Subjects in Harmony TPV study						
Evaluation	**Subjects in Native EFS study (N = 21)**	**TPV 22 (N = 21)**	**cTPV 25 (N = 19)**	**mTPV 25 (N = 10)**	**TPV 22 + mTPV 25 (N = 31)**	**All subjects in Harmony TPV study (N = 50)**	**Native EFS + TPV 22 + mTPV 25 (N = 52)**	**All subjects in 2 studies combined (N = 71)**
Sex								
Female	47.6% (10/21)	47.6% (10/21)	26.3% (5/19)	40.0% (4/10)	45.2% (14/31)	38.0% (19/50)	46.2% (24/52)	40.8% (29/71)
Male	52.4% (11/21)	52.4% (11/21)	73.7% (14/19)	60.0% (6/10)	54.8% (17/31)	62.0% (31/50)	53.8% (28/52)	59.2% (42/71)
Baseline age (years)								
Median (min, max)	25 (12, 57)	26 (12, 43)	24 (12, 59)	36 (18, 50)	29 (12, 50)	27.5 (12, 59)	29 (12, 57)	27 (12, 59)
Body weight (kg)								
Median (min, max)	66.5 (34.1, 116.7)	61.7 (42.2, 130.0)	76.8 (36.5, 121.0)	76.1 (54.9, 85.1)	68.3 (42.2, 130.0)	69.5 (36.5, 130.0)	66.8 (34.1, 130.0)	68.3 (34.1, 130.0)
Original diagnosis								
Tetralogy of Fallot	95.2% (20/21)	95.2% (20/21)	84.2% (16/19)	70.0% (7/10)	87.1% (27/31)	86.0% (43/50)	90.4% (47/52)	88.7% (63/71)[2]
With pulmonary stenosis	100.0% (20/20)	65.0% (13/20)	37.5% (6/16)	57.1% (4/7)	63.0% (17/27)	53.5% (23/43)	78.7% (37/47)	68.3% (43/63)
With pulmonary atresia	0.0% (0/20)	10.0% (2/20)	12.5% (2/16)	14.3% (1/7)	11.1% (3/27)	11.6% (5/43)	6.4% (3/47)	7.9% (5/63)
Absent pulmonary valve	0.0% (0/20)	0.0% (0/20)	0.0% (0/16)	0.0% (0/7)	0.0% (0/27)	0.0% (0/43)	0.0% (0/47)	0.0% (0/63)
Pulmonary stenosis	NA	0.0% (0/21)	5.3% (1/19)	20.0% (2/10)	6.5% (2/31)	6.0% (3/50)	6.5% (2/31)	6.0% (3/50)
Pure pulmonary atresia (pulmonary atresia with intact ventricular septum)	NA	0.0% (0/21)	5.3% (1/19)	0.0% (0/10)	0.0% (0/31)	2.0% (1/50)	0.0% (0/31)	2.0% (1/50)
Transposition of the great vessels	0.0% (0/21)	0.0% (0/21)	0.0% (0/19)	0.0% (0/10)	0.0% (0/31)	0.0% (0/50)	0.0% (0/52)	0.0% (0/71)
Truncus arteriosus	0.0% (0/21)	0.0% (0/21)	0.0% (0/19)	0.0% (0/10)	0.0% (0/31)	0.0% (0/50)	0.0% (0/52)	0.0% (0/71)
Branch pulmonary artery stenosis	0.0% (0/21)	NA	NA	NA	NA	NA	0.0% (0/21)	0.0% (0/21)
Other diagnosis[1]	14.3% (3/21)	4.8% (1/21)	5.3% (1/19)	10.0% (1/10)	6.5% (2/31)	6.0% (3/50)	9.6% (5/52)	8.5% (6/71)
Type of surgical patch materials								
None	0.0% (0/15)	20.0% (4/20)	10.5% (2/19)	20.0% (2/10)	20.0% (6/30)	16.3% (8/49)	13.3% (6/45)	12.5% (8/64)
Dacron	6.7% (1/15)	5.0% (1/20)	0.0% (0/19)	0.0% (0/10)	3.3% (1/30)	2.0% (1/49)	4.4% (2/45)	3.1% (2/64)
Gore-Tex	20.0% (3/15)	0.0% (0/20)	0.0% (0/19)	0.0% (0/10)	0.0% (0/30)	0.0% (0/49)	6.7% (3/45)	4.7% (3/64)
Autologous pericardium	40.0% (6/15)	10.0% (2/20)	0.0% (0/19)	0.0% (0/10)	6.7% (2/30)	4.1% (2/49)	17.8% (8/45)	12.5% (8/64)
Bovine pericardium	6.7% (1/15)	5.0% (1/20)	0.0% (0/19)	0.0% (0/10)	3.3% (1/30)	2.0% (1/49)	4.4% (2/45)	3.1% (2/64)
Unknown	26.7% (4/15)	45.0% (9/20)	42.1% (8/19)	60.0% (6/10)	50.0% (15/30)	46.9% (23/49)	42.2% (19/45)	42.2% (27/64)
Other	0.0% (0/15)	15.0% (3/20)	47.4% (9/19)	20.0% (2/10)	16.7% (5/30)	28.6% (14/49)	11.1% (5/45)	21.9% (14/64)
Pacemaker or ICD implant	14.3% (3/21)	4.8% (1/21)	5.3% (1/19)	20.0% (2/10)	9.7% (3/31)	8.0% (4/50)	11.5% (6/52)	9.9% (7/71)

		Subjects in Harmony TPV study						
Evaluation	**Subjects in Native EFS study (N = 21)**	**TPV 22 (N = 21)**	**cTPV 25 (N = 19)**	**mTPV 25 (N = 10)**	**TPV 22 + mTPV 25 (N = 31)**	**All subjects in Harmony TPV study (N = 50)**	**Native EFS + TPV 22 + mTPV 25 (N = 52)**	**All subjects in 2 studies combined (N = 71)**
Pulmonary regurgitation by echocardiography								
None	0.0% (0/21)	0.0% (0/21)	0.0% (0/19)	0.0% (0/10)	0.0% (0/31)	0.0% (0/50)	0.0% (0/52)	0.0% (0/71)
Minor	0.0% (0/21)	0.0% (0/21)	0.0% (0/19)	0.0% (0/10)	0.0% (0/31)	0.0% (0/50)	0.0% (0/52)	0.0% (0/71)
Mild	0.0% (0/21)	0.0% (0/21)	0.0% (0/19)	0.0% (0/10)	0.0% (0/31)	0.0% (0/50)	0.0% (0/52)	0.0% (0/71)
Moderate	4.8% (1/21)	4.8% (1/21)	5.3% (1/19)	0.0% (0/10)	3.2% (1/31)	4.0% (2/50)	3.8% (2/52)	4.2% (3/71)
Severe	95.2% (20/21)	95.2% (20/21)	94.7% (18/19)	100.0% (10/10)	96.8% (30/31)	96.0% (48/50)	96.2% (50/52)	95.8% (68/71)
Mean right ventricular outflow tract gradient (mmHg) by echocardiography								
N	21	17	14	4	21	35	42	56
Mean ± SD	10.5 ± 5.0	10.3 ± 6.4	9.0 ± 4.4	4.9 ± 3.1	9.2 ± 6.2	9.1 ± 5.5	9.9 ± 5.6	9.7 ± 5.3
Number of previous open heart surgeries								
N	21	21	19	10	31	50	52	71
Mean ± SD	1.2 ± 0.4	1.4 ± 0.6	1.2 ± 0.5	1.4 ± 0.5	1.4 ± 0.6	1.3 ± 0.5	1.3 ± 0.5	1.3 ± 0.5
Medical history of endocarditis	NA	4.8% (1/21)	0.0% (0/19)	0.0% (0/10)	3.2% (1/31)	2.0% (1/50)	3.2% (1/31)	2.0% (1/50)

[1] Patients with "other diagnosis" as the original diagnosis had the following: double-outlet right ventricle (DORV), atrial septal defect, DORV with pulmonary stenosis, "absent" left pulmonary artery, Noonan syndrome, and dysplastic pulmonary stenosis, or variant of tetralogy of Fallot (DORV with pulmonary stenosis, secundum atrial septal defect, and patent ductus arteriosus).

[2] Of the patients with tetralogy of Fallot (63 of 71 subjects), 2 are also classified as "other diagnosis," as shown below:

- Native EFS Patient 1: tetralogy of Fallot + other diagnosis ("absent" left pulmonary artery)
- Native EFS Patient 2: tetralogy of Fallot + other diagnosis (atrial septal defect)

6.A.(2) Results for primary endpoint

6.A.(2).1) Efficacy

The primary efficacy endpoint, "percentage of subjects with acceptable hemodynamic function at 6 months" was evaluated using the Core lab data. The analysis cohort was the Implanted >24 Hours Cohort[ii] at 6 months after the index procedure. The primary objective for efficacy was to be analyzed using descriptive statistics. It was defined that the primary efficacy endpoint would be met if the point estimate of the percentage of subjects with acceptable hemodynamic function at 6 months is ≥75%, the performance target. Acceptable hemodynamic function was defined as conditions meeting all of the following requirements:

(1) Mean right ventricular outflow tract gradient as measured by echocardiography ≤40 mmHg;
(2) Pulmonary regurgitant fraction as measured by MRI <20% or pulmonary regurgitation as measured by echocardiography is less than moderate in severity;
(3) No TPV reinterventions

In the cohort for the primary analysis, the percentage of subjects with acceptable hemodynamic function at 6 months was 89.2% (95% CI, 79.1%–95.6%), which is ≥75%, the performance target (Table 7).

Three subjects in the Harmony TPV study implanted with an mTPV 25 (proposed device; see Table 1) were excluded from the primary analysis because their echocardiography data were not evaluable. Among subjects who had not achieved acceptable hemodynamic function, 2 in the Native EFS study underwent explantation of TPV before the 6-month visit. In the Harmony TPV study, 3 subjects implanted with cTPV 25 (predecessor model; see Table 1) had reintervention. In addition, 1 subject implanted with cTPV 25 (predecessor model) presented with severe pulmonary regurgitation, and another subject implanted with mTPV 25 (proposed device) presented with moderate pulmonary regurgitation.

[ii] The Implanted >24 Hours Cohort consisted of all subjects who underwent catheterization and had a Harmony TPV that remained implanted for >24 hours.

Table 7. Subjects with acceptable TPV hemodynamic function at 6 months post-implant—Implanted >24 Hours Cohort, primary analysis

		Subjects in Harmony TPV study						
Type of analysis	**Subjects in Native EFS study (N = 20)**	**TPV 22 (N = 21)**	**cTPV 25 (N = 17)**	**mTPV 25 (N = 10)**	**TPV 22 + mTPV 25 (N = 31)**	**All subjects in Harmony TPV study (N = 48)**	**Native EFS + TPV 22 + mTPV 25 (N = 51)**	**All subjects in 2 studies combined (N = 68)**
Primary analysis								
Number of subjects analyzed	20	21	17	7	28	45	48	65
Number and percentage of subjects with acceptable TPV hemodynamic function	18 (90.0%)	21 (100.0%)	13 (76.5%)	6 (85.7%)	27 (96.4%)	40 (88.9%)	45 (93.8%)	58 (89.2%)
Standard error	6.7%	0.0%	10.3%	13.2%	3.5%	4.7%	3.5%	3.8%
Two-sided 95% CI[1]	68.3%–98.8%	83.9%–100.0%	50.1%–93.2%	42.1%–99.6%	81.7%–99.9%	75.9%–96.3%	82.8%–98.7%	79.1%–95.6%
Was target met?[2]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[1] Two-sided Clopper-Pearson interval.
[2] The primary efficacy endpoint would be met if the point estimate is ≥75%, the performance target.

6.A.(2).2) Safety

The primary safety endpoint, "freedom from procedure- or device-related mortality at 30 days post-implantation" was evaluated using data that were adjudicated by a Clinical Events Committee (CEC), and the TPV Catheterized Cohort was used as the analysis cohort. The primary objective for safety was to be analyzed using descriptive statistics. It was defined that the primary safety endpoint would be met if the point estimate of the percentage of the freedom from procedure- or device-related mortality at 30 days post-implant is ≥95%, the performance target.

There were no deaths at 30 days post-implant both in either the Native EFS study or Harmony TPV study (Native EFS study, 0% [0 of 21 subjects]; Harmony TPV study, 0% [0 of 50 subjects]), showing that the results of the primary safety endpoint exceeded the performance target.

6.A.(3) Secondary endpoints

6.A.(3).1) Echocardiography (Core lab data)

Table 8 shows the results of echocardiography (Core lab data) in subjects in the Native EFS and Harmony TPV studies who completed implantation (Implanted Cohort).[iii] The mean right ventricular outflow tract gradient measured by echocardiography at 6 months post-implant was 14.0 ± 5.3 mmHg. The percentage of subjects who presented with moderate or greater pulmonary regurgitation was 5% (3 of 60 subjects) at 6 months post-implant and 7.4% (4 of 54 subjects) at 1 year post-implant. The percentage of subjects who presented with moderate or greater paravalvular leak was 3.4% (2 of 58 subjects) at 6 months post-implant and 5.7% (3 of 53 subjects; 2 of them had a cTPV 25 [predecessor model]) at 1 year post-implant.

[iii] The Implanted Cohort consisted of all subjects who underwent catheterization and implantation of a Harmony TPV.

Table 8. Summary of echocardiography data at visits (Core lab data)—Implanted Cohort (N = 70)

Measurement	Pre-implant (N = 69)	Discharged (N = 67)	1 month (N = 64)	6 months (N = 63)	1 year (N =54)	2 years[1] (N = 28)	3 years[2] (N = 17)
Pulmonary regurgitation							
Absent	0.0% (0/64)	64.2% (43/67)	70.3% (45/64)	81.7% (49/60)	72.2% (39/54)	75.0% (21/28)	81.3% (13/16)
Minor	0.0% (0/64)	16.4% (11/67)	20.3% (13/64)	8.3% (5/60)	16.7% (9/54)	17.9% (5/28)	18.8% (3/16)
Mild	0.0% (0/64)	16.4% (11/67)	6.3% (4/64)	5.0% (3/60)	3.7% (2/54)	3.6% (1/28)	0.0% (0/16)
Moderate	15.6% (10/64)	0.0% (0/67)	3.1% (2/64)	3.3% (2/60)	7.4% (4/54)	3.6% (1/28)	0.0% (0/16)
Severe	84.4% (54/64)	3.0% (2/67)	0.0% (0/64)	1.7% (1/60)	0.0% (0/54)	0.0% (0/28)	0.0% (0/16)
Paravalvular leak							
Absent	NA	79.7% (47/59)	77.8% (49/63)	87.9% (51/58)	79.2% (42/53)	81.5% (22/27)	87.5% (14/16)
Minor	NA	6.8% (4/59)	15.9% (10/63)	3.4% (2/58)	11.3% (6/53)	14.8% (4/27)	12.5% (2/16)
Mild	NA	11.9% (7/59)	4.8% (3/63)	5.2% (3/58)	3.8% (2/53)	0.0% (0/27)	0.0% (0/16)
Moderate	NA	0.0% (0/59)	1.6% (1/63)	3.4% (2/58)	5.7% (3/53)	3.7% (1/27)	0.0% (0/16)
Severe	NA	1.7% (1/59)	0.0% (0/63)	0.0% (0/58)	0.0% (0/53)	0.0% (0/27)	0.0% (0/16)
Mean right ventricular outflow tract gradient (mmHg) by echocardiography							
N	65	64	62	61	54	28	17
Mean ± SD	9.1 ± 4.1	13.5 ± 6.3	13.3 ± 6.9	14.0 ± 5.3	15.7 ± 6.0	18.1 ± 6.4	15.9 ± 5.2
Maximum right ventricular outflow tract gradient (mmHg) calculated from continuous-wave Doppler data							
N	65	64	62	61	54	28	17
Mean ± SD	16.5 ± 7.5	23.4 ± 10.5	22.3 ± 10.6	24.3 ± 8.7	27.4 ± 10.0	31.1 ± 9.6	27.2 ± 9.5
Maximum velocity of the right ventricular outflow tract (m/s)							
N	65	64	62	61	54	28	17
Mean ± SD	2.0 ± 0.5	2.4 ± 0.5	2.3 ± 0.5	2.4 ± 0.4	2.6 ± 0.5	2.8 ± 0.4	2.6 ± 0.4
Tricuspid regurgitation							
Absent	0.0% (0/65)	0.0% (0/64)	0.0% (0/62)	0.0% (0/59)	2.0% (1/49)	3.6% (1/28)	0.0% (0/15)
Minor	21.5% (14/65)	21.9% (14/64)	33.9% (21/62)	37.3% (22/59)	40.8% (20/49)	50.0% (14/28)	53.3% (8/15)
Mild	61.5% (40/65)	64.1% (41/64)	46.8% (29/62)	50.8% (30/59)	53.1% (26/49)	39.3% (11/28)	46.7% (7/15)
Moderate	16.9% (11/65)	12.5% (8/64)	16.1% (10/62)	10.2% (6/59)	2.0% (1/49)	7.1% (2/28)	0.0% (0/15)
Severe	0.0% (0/65)	1.6% (1/64)	3.2% (2/62)	1.7% (1/59)	2.0% (1/49)	0.0% (0/28)	0.0% (0/15)
Maximum velocity of tricuspid regurgitant jet (m/sec)							
N	55	46	55	52	43	23	10
Mean ± SD	2.5 ± 0.4	2.7 ± 0.4	2.7 ± 0.5	2.6 ± 0.4	2.7 ± 0.5	2.8 ± 0.6	2.8 ± 0.4

[1] Eleven of the 28 subjects are participants in the Harmony TPV study
[2] Two of the 17 subjects are participants in the Harmony TPV study

6.A.(3).2) Technical success at exit from catheterization lab/operating room

The overall technical success[iv] rate in the Attempted Implant Cohort[v] in the Native EFS study and the Harmony TPV study was 92.9% (65 of 70 subjects). All of the 5 subjects who did not meet the criteria for technical success had received cTPV 25 (predecessor model). Of the 5 subjects, 3 did not meet the criterion "deployment and correct positioning (including minor repositioning if needed) of the single intended device," and 3 did not meet the criterion "no unplanned or emergency surgery or reintervention related to the device or access procedure" (one of the 5 subjects did not meet either of the requirement).

6.A.(3).3) Procedural success at 30 days

The overall procedural success[vi] rate at 30 days in the Attempted Implant Cohort (n = 50) from the Harmony TPV study was 84.0% (42 of 50 subjects). The 8 subjects who did not achieve procedural success were all due to device failure (7 received cTPV 25 [predecessor model] and 1 received cTPV 22 [predecessor model]). In addition, 1 subject (cTPV 25) did not meet the criterion "no major vascular or cardiac structural complications required unplanned reintervention or surgery."

6.A.(3).4) Evaluation of right ventricle remodeling as assessed by MRI

Right ventricle remodeling post-implant in the Native EFS study and Harmony TPV study was characterized by MRI only in subjects for whom MRI was not contraindicated. MRI was performed in implanted subjects at pre-implant and 1 year post-implant in the Native EFS study and at pre-implant and 6 months and 2 years post-implant in the Harmony TPV study. The mean RVEDV, RVEDVi, right ventricular end-systolic volume (RVESV), pulmonary regurgitant fraction (PRF), and right ventricular ejection fraction (RVEF) decreased post-implant (Table 9).

[iv] Technical success is defined as "no device- or procedure-related mortality," "successful access, delivery and retrieval of the delivery system," "deployment and correct positioning (including minor repositioning if needed) of the single intended device," "no need for additional unplanned or emergency surgery or re-intervention related to the device or access procedure."

[v] The Attempted Implant Cohort consisted of all subjects who underwent catheterization and Harmony TPV implantation was attempted (a Harmony TPV was inserted into the subject's body).

[vi] Procedural success is defined as "no device failure," "no life-threatening major bleed," "no major vascular or cardiac structural complications required unplanned reintervention or surgery," "no stage 2 or 3 acute kidney injury (including new dialysis)," "no pulmonary embolism," "no severe heart failure or hypotension requiring intravenous inotrope, ultrafiltration, or mechanical circulatory support," "intubation (≤48 hours)." Procedural success was evaluated based on these 7 criteria. In the Native EFS study, "procedural success at 30 days" was not included in the analysis of the secondary endpoints because data on intubation duration were not collected.

Table 9. Evaluation of right ventricle remodeling as assessed by MRI

	Native EFS study		Harmony TPV study		
Measurement	**Pre-implant (N = 17)**	**1 year (N = 14)**	**Pre-implant (N = 43)**	**6 months (N = 33)**	**2 years (N = 6)**
MRI					
RVEDV (mL)					
N	16	13	37	30	6
Median	281.0	177.0	284.0	221.2	178.0
Min, Max	120.7, 472.3	74.0, 251.0	170.2, 438.8	124.0, 349.5	116.0, 263.0
RVEDV index (mL/m^2)					
N	16	13	36	30	6
Median	160.8	94.7	158.0	114.9	106.2
Min, Max	111.8, 253.6	67.3, 146.0	115.0, 220.5	88.5, 221.2	64.4, 133.5
RVESV (mL)					
N	16	13	37	30	6
Median	130.6	96.0	157.0	119.5	112.0
Min, Max	50.4, 268.2	33.0, 163.0	86.2, 264.9	55.0, 231.6	69.0, 147.0
PRF (%)					
N	11	10	32	28	6
Median	42.2	2.0	42.4	0.9	0.6
Min, Max	1.1, 53.2	0.0, 7.2	23.3, 72.1	0.0, 13.0	0.0, 4.9
RVEF (%)					
N	16	13	37	30	6
Median	50.6	46.3	45.6	44.9	39.9
Min, Max	35.6, 61.5	31.5, 58.4	36.3, 66.2	29.4, 55.7	31.5, 51.6

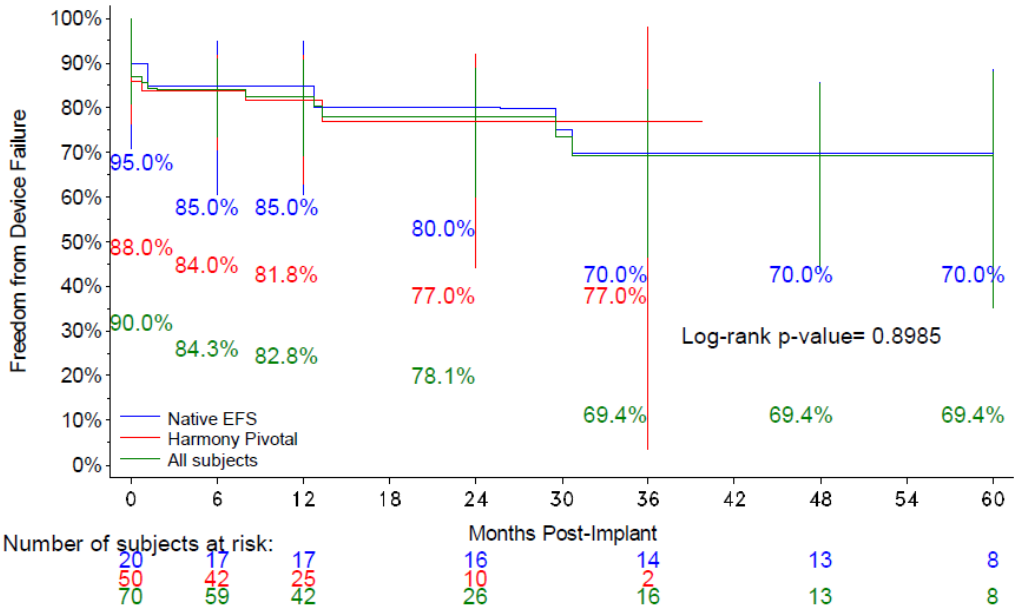
6.A.(3).5) Characterization of QOL score over time

Quality of life was assessed in the Implanted >24 Hours Cohort of the Harmony TPV study using the Short Form 36-item Health Survey (SF-36). The mean score of physical functioning increased from 80.5 ± 25.6 (baseline) to 91.3 ± 16.2 (1 year post-implant), showing a moderate degree of improvement in QOL. The QOL in subjects of the Native EFS study was not assessed because QOL assessment was not included in the study protocol.

6.A.(4) Long-term data

Figure 5 shows the Kaplan-Meier estimate for freedom from device failure[vii] in the Attempted Implant Cohort. The rate of freedom from device failure at 5 years post-implant was 69.4%. Figure 6 shows the Kaplan-Meier estimate for freedom from device failure in subjects in whom implantation of the TPV 22 earlier model, cTPV 22 (predecessor model), or mTPV 25 (proposed device) was attempted (cTPV 25 [predecessor model] was excluded).

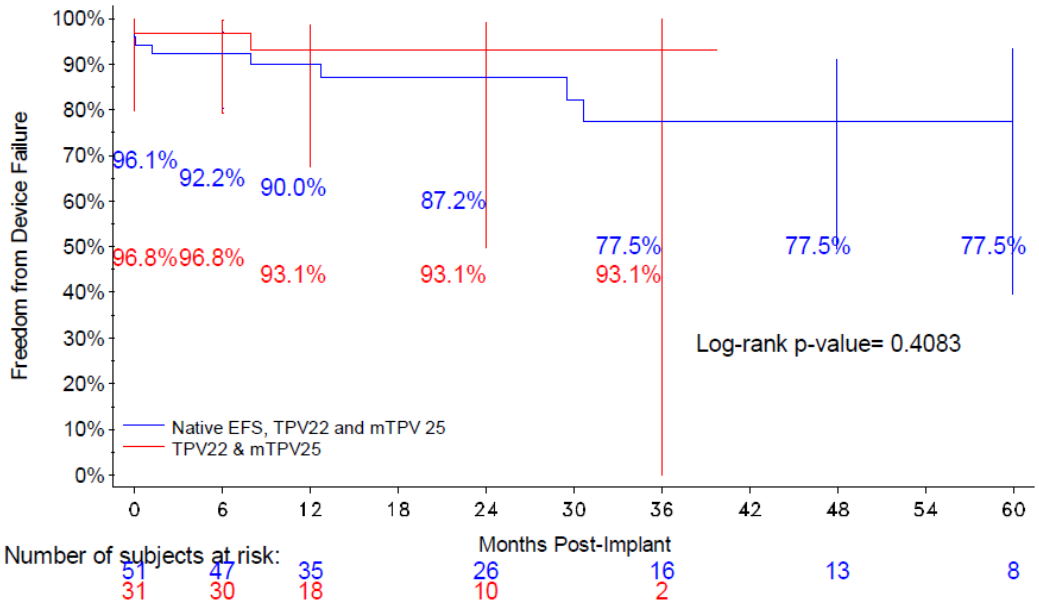
[vii] Freedom from device failure is defined as follows: "no device- or procedural-related mortality," "original intended device in place," "no additional surgical or interventional procedures related to access or the device since completion of the original procedure (i.e., exit from the catheterization lab)," "intended performance of the device, namely, no migration, embolization, detachment, major stent fracture, hemolysis, thrombosis, or endocarditis," "relief of insufficiency (less than moderate pulmonary regurgitation) without producing the opposite (i.e., mean right ventricular outflow tract gradient >40 mmHg) as measured by continuous-wave Doppler echocardiography," "absence of para-device complications (moderate or greater paravalvular leak, erosion, right ventricular outflow tract or pulmonary artery rupture)."



	Months post-implant[1]							
	0	**1**	**6**	**12**	**24**	**36**	**48**	**60**
Native EFS study (N = 20)								
Number of subjects at the end of the month	20	18	17	17	16	14	13	8
Number of events during the month	1	1	1	0	1	2	0	0
Cumulative number of events	1	2	3	3	4	6	6	6
Number censored within the interval	0	0	0	0	0	0	1	5
Cumulative number censored	0	0	0	0	0	0	1	6
K-M estimate of freedom from events (%)	95.0	90.0	85.0	85.0	80.0	70.0	70.0	70.0
Lower bound of 95% CI	70.7	65.6	60.4	60.4	55.1	45.1	44.0	35.6
Upper bound of 95% CI	99.2	97.4	94.9	94.9	92.0	85.3	85.7	88.4
Harmony TPV study (N = 50)								
Number of subjects at the end of the month	50	42	42	25	10	2	0	0
Number of events during the month	6	2	0	1	1	0	0	0
Cumulative number of events	6	8	8	9	10	10	10	10
Number censored within the interval	0	0	0	16	14	8	2	0
Cumulative number censored	0	0	0	16	30	38	40	40
K-M estimate of freedom from events (%)	88.0	84.0	84.0	81.8	77.0	77.0	NA	NA
Lower bound of 95% CI	76.3	70.5	70.5	63.0	44.2	3.6	NA	NA
Upper bound of 95% CI	94.1	91.7	91.7	91.6	91.9	98.0	NA	NA
All subjects (N = 70)								
Number of subjects at the month	70	60	59	42	26	16	13	8
Number of events within the interval	7	3	1	1	2	2	0	0
Cumulative number of events	7	10	11	12	14	16	16	16
Number censored within the interval	0	0	0	16	14	8	3	5
Cumulative number censored	0	0	0	16	30	38	41	46
K-M estimate of freedom from events (%)	90.0	85.7	84.3	82.8	78.1	69.4	69.4	69.4
Lower bound of 95% CI	80.8	75.1	73.4	69.2	59.9	46.4	43.5	35.2
Upper bound of 95% CI	94.9	92.0	91.0	90.7	88.7	84.0	85.2	88.0

[1] 0 months (0 days); 1 month (1–30 days); 6 months (31–183 days); 12 months (184–365 days); 24 months (366–730 days); 36 months (731–1,095 days); 48 months (1,096–1,460 days); and 60 months (1,461–1,825 days).
The cumulative probability of freedom from event estimate was based on the Kaplan-Meier (K-M) method. The 95% confidence interval was the log-log-transformed 95% confidence interval using the Peto standard error.

Figure 5. Kaplan-Meier estimate for freedom from device failure—Attempted Implant Cohort



	Months post-implant[1]							
	0	**1**	**6**	**12**	**24**	**36**	**48**	**60**
Native EFS + TPV 22 + mTPV 25 (N = 51)								
Number of subjects at the end of the month	51	48	47	35	26	16	13	8
Number of events during the month	2	1	1	1	1	2	0	0
Cumulative number of events	2	3	4	5	6	8	8	8
Number censored within the interval	0	0	0	11	8	8	3	5
Cumulative number censored	0	0	0	11	19	27	30	35
K-M estimate of freedom from events (%)	96.1	94.1	92.2	90.0	87.2	77.5	77.5	77.5
Lower bound of 95% CI	85.6	82.9	80.4	75.2	68.8	53.0	49.6	39.6
Upper bound of 95% CI	99.0	98.1	97.0	96.2	95.1	90.3	91.2	93.2
TPV 22 + mTPV 25 (N = 31)								
Number of subjects at the end of the month	31	30	30	18	10	2	0	0
Number of events during the month	1	0	0	1	0	0	0	0
Cumulative number of events	1	1	1	2	2	2	2	2
Number censored within the interval	0	0	0	11	8	8	2	0
Cumulative number censored	0	0	0	11	19	27	29	29
K-M estimate of freedom from events (%)	96.8	96.8	96.8	93.1	93.1	93.1	NA	NA
Lower bound of 95% CI	79.8	79.2	79.2	67.7	49.9	0.0	NA	NA
Upper bound of 95% CI	99.5	99.5	99.5	98.7	99.3	100.0	NA	NA

[1] 0 months (0 days); 1 month (1–30 days); 6 months (31–183 days); 12 months (184–365 days); 24 months (366–730 days); 36 months (731–1,095 days); 48 months (1,096–1,460 days); and 60 months (1,461–1,825 days).
The cumulative probability of freedom from event estimate was based on the Kaplan-Meier (K-M) method. The 95% confidence interval was the log-log-transformed 95% confidence interval using the Peto standard error.

Figure 6. Kaplan-Meier estimate for freedom from device failure—Attempted Implant Cohort (TPV 22 or mTPV 25) in Native EFS study

6.A.(5) Adverse events

6.A.(5).1) Adverse events

Table 10 summarizes all CEC-adjudicated adverse events (as of [redacted], 20[redacted]) that occurred in subjects of the TPV Catheterized Cohort from the Native EFS study and the Harmony TPV study. No hospital readmissions due to cardiac failure were reported.

Table 10. Summary of CEC-adjudicated adverse events—TPV Catheterized Cohort (N = 71)

			Harmony TPV study subjects							
	Native EFS (N = 21)		TPV 22 + mTPV 25 (N = 31)		Harmony TPV total (N = 50)		Native EFS + TPV 22 + mTPV 25 (N = 52)		Overall subjects (N = 71)	
CEC-adjudicated adverse events	**Events**	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**
Subjects with CEC-adjudicated adverse events	31	57.1% (12/21)	17	45.2% (14/31)	39	54.0% (27/50)	48	50.0% (26/52)	70	54.9% (39/71)
Brachial plexus injury	0	0.0% (0/21)	1	3.2% (1/31)	1	2.0% (1/50)	1	1.9% (1/52)	1	1.4% (1/71)
Cardiac arrest	1	4.8% (1/21)	0	0.0% (0/31)	0	0.0% (0/50)	1	1.9% (1/52)	1	1.4% (1/71)
Congestive heart failure	2	4.8% (1/21)	0	0.0% (0/31)	0	0.0% (0/50)	2	1.9% (1/52)	2	1.4% (1/71)
Embolization of the TPV	0	0.0% (0/21)	0	0.0% (0/31)	2	4.0% (2/50)	0	0.0% (0/52)	2	2.8% (2/71)
Erosion	1	4.8% (1/21)	0	0.0% (0/31)	0	0.0% (0/50)	1	1.9% (1/52)	1	1.4% (1/71)
Heart block third degree	0	0.0% (0/21)	0	0.0% (0/31)	1	2.0% (1/50)	0	0.0% (0/52)	1	1.4% (1/71)
Hemorrhage: mild	0	0.0% (0/21)	3	9.7% (3/31)	5	10.0% (5/50)	3	5.8% (3/52)	5	7.0% (5/71)
Migration of TPV	2	9.5% (2/21)	1	3.2% (1/31)	1	2.0% (1/50)	3	5.8% (3/52)	3	4.2% (3/71)
Misplacement of TPV	0	0.0% (0/21)	0	0.0% (0/31)	1	2.0% (1/50)	0	0.0% (0/52)	1	1.4% (1/71)
Paravalvular leak: Severe	1	4.8% (1/21)	0	0.0% (0/31)	0	0.0% (0/50)	1	1.9% (1/52)	1	1.4% (1/71)
Paravalvular leak: Mild	1	4.8% (1/21)	1	3.2% (1/31)	5	10.0% (5/50)	2	3.8% (2/52)	6	8.5% (6/71)
Pseudoaneurysm	0	0.0% (0/21)	1	3.2% (1/31)	1	2.0% (1/50)	1	1.9% (1/52)	1	1.4% (1/71)
Stent fracture: severe	1	4.8% (1/21)	0	0.0% (0/31)	0	0.0% (0/50)	1	1.9% (1/52)	1	1.4% (1/71)
Structural deterioration	3	9.5% (2/21)	0	0.0% (0/31)	0	0.0% (0/50)	3	3.8% (2/52)	3	2.8% (2/71)
Supraventricular tachycardia	0	0.0% (0/21)	2	6.5% (2/31)	2	4.0% (2/50)	2	3.8% (2/52)	2	2.8% (2/71)
Upper respiratory tract infection	1	4.8% (1/21)	0	0.0% (0/31)	0	0.0% (0/50)	1	1.9% (1/52)	1	1.4% (1/71)
Valve dysfunction: Regurgitation	1	4.8% (1/21)	0	0.0% (0/31)	1	2.0% (1/50)	1	1.9% (1/52)	2	2.8% (2/71)
Valve dysfunction: stenosis	6	23.8% (5/21)	0	0.0% (0/31)	0	0.0% (0/50)	6	9.6% (5/52)	6	7.0% (5/71)
Ventricular extrasystoles	0	0.0% (0/21)	2	6.5% (2/31)	4	8.0% (4/50)	2	3.8% (2/52)	4	5.6% (4/71)
Ventricular tachycardia	1	4.8% (1/21)	4	12.9% (4/31)	9	18.0% (9/50)	5	9.6% (5/52)	10	14.1% (10/71)
Other	2	4.8% (1/21)	0	0.0% (0/31)	0	0.0% (0/50)	2	1.9% (1/52)	2	1.4% (1/71)
Other cardiac events	2	4.8% (1/21)	0	0.0% (0/31)	0	0.0% (0/50)	2	1.9% (1/52)	2	1.4% (1/71)
Other central nervous system	3	4.8% (1/21)	0	0.0% (0/31)	0	0.0% (0/50)	3	1.9% (1/52)	3	1.4% (1/71)

	Native EFS (N = 21)		Harmony TPV study subjects				Native EFS + TPV 22 + mTPV 25 (N = 52)		Overall subjects (N = 71)	
			TPV 22 + mTPV 25 (N = 31)		Harmony TPV total (N = 50)					
CEC-adjudicated adverse events	**Events**	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**
Other device-related adverse events	1	4.8% (1/21)	0	0.0% (0/31)	4	8.0% (4/50)	1	1.9% (1/52)	5	7.0% (5/71)
Other hematological/oncological events	1	4.8% (1/21)	0	0.0% (0/31)	0	0.0% (0/50)	1	1.9% (1/52)	1	1.4% (1/71)
Other implantation/catheterization-related events	0	0.0% (0/21)	2	6.5% (2/31)	2	4.0% (2/50)	2	3.8% (2/52)	2	2.8% (2/71)
Other kidney-related events	1	4.8% (1/21)	0	0.0% (0/31)	0	0.0% (0/50)	1	1.9% (1/52)	1	1.4% (1/71)

6.A.(5).2) Death

No deaths were reported in the Harmony TPV study. One patient died during the long-term follow-up period of the Native EFS study. This patient (aged ■ years; original diagnosis, tetralogy of Fallot with pulmonary stenosis; medical history, coronary artery disease) died of cardiac arrest at 1,311 days post-implant. According to the study center's report, the patient died suddenly at work. Autopsy was not performed and the study center was not able to obtain further information. During the 3-year follow-up period, the TPV in this patient had been assessed by the echocardiography Core lab as mean right ventricular outflow tract gradient of ≤14.7 mmHg with no or minor pulmonary regurgitation; this means that the pulmonary valve function had been maintained. At 1 month post-implant, a diagnostic catheterization was performed in this patient because the patient complained of chest discomfort following Harmony TPV implant and because the patient had a medical history of coronary artery disease. The catheterization did not indicate any change in the coronary arteries, and further intervention was not needed.

6.A.(5).3) Surgical interventions (TPV explantation)

In the Native EFS study and Harmony TPV study, TPV was explanted from 4 subjects. Table 11 summarizes the cases.

Table 11. Summary of surgical interventions (TPV explantation)

	Study/device	Summary
Patient 1	Native EFS / TPV 22 earlier model	Although no complications occurred during the implant procedure, the subject complained of fatigue at 1 month follow-up and was found to have an upper respiratory tract infection. Radiography identified fragments of valve frame that were broken towards the inside of the valve region. The TPV was successfully explanted and replaced with a 25-mm bioprosthetic valve (at 40 days post-implant). No serious complications were reported in the surgery. The pathology Core lab reported that the valve frame was fractured and the inflow end of the device within the fractured region was waving.
Patient 2	Native EFS / TPV 22 earlier model	Although no complications occurred during the implant procedure, discharge echocardiography at 1 day post-implant showed evidence that the device had migrated to the main pulmonary artery and was in an unstable condition. This subject presented with mild pulmonary regurgitation and moderate paravalvular leak secondary to migration. The TPV was explanted at 2 days post-implant and a

	Study/device	Summary
		Hancock conduit (26 mm) was surgically implanted, with no serious complications. The surgery revealed that valve frame fracture caused partial erosion of the subject's intrinsic anatomy in the area of bifurcation of the pulmonary trunk.
Patient 3	Harmony TPV/ cTPV 25 (predecessor model)	Implant was challenging in this subject. The first valve was removed because part of the valve was positioned lower than intended. A reimplantation was attempted but resulted in migration of the valve toward the right ventricle. The subject was moved to an operation room where the valve was removed, followed by surgical valve placement. The subject was discharged in a stable condition.
Patient 4	Harmony TPV/ cTPV 25 (predecessor model)	Implant was challenging in this subject. The valve migrated toward the right ventricle during the final placement and release. The patient was in a stable condition, but the surgeon was not sure of the long-term stability of the TPV. Surgical valve replacement was performed on the following day. The subject was discharged in a stable condition.

6.A.(5).4) Percutaneous reintervention

In the Native EFS study and Harmony TPV study, 14 percutaneous reinterventions were performed in 6 subjects. Some subjects had more than one type of percutaneous reintervention. Table 12 summarizes the reinterventions.

Table 12. Summary of percutaneous reinterventions

	Study/device	Summary
Patient 1	Native EFS/ TPV 22 earlier model	No complications occurred during the implant procedure, but echocardiography at the 1-year visit indicated moderate to severe pulmonary stenosis (mean right ventricular outflow tract gradient of 33 mmHg). A diagnostic catheterization was performed to evaluate hemodynamic function. The mean right ventricular outflow tract gradient was 15 mmHg, and intervention was not required. Pulmonary stenosis was not indicated by echocardiography at the 5-year visit (mean right ventricular outflow tract gradient of 21 mmHg).
Patient 2	Native EFS/ TPV 22 earlier model	No complications occurred during the implant procedure, but echocardiography at the 2-year visit indicated moderate pulmonary regurgitation with an elevated mean right ventricular outflow tract gradient (23 mmHg). A CT examination indicated high levels in RVEDVi (170.5 mL/m^2), RVEF (38%), and pulmonary regurgitant fraction (33%). At 881 days post-implant, after performing a series of balloon angioplasty procedures, a bare metal stent and then the Melody TPV were implanted. Furthermore, a patent foramen ovale was found, and was occluded with a 25-mm Amplatzer Cribriform (atrial septal defect closure device). At the 5-year visit, pulmonary regurgitation was not detected by echocardiography, with a mean right ventricular outflow tract gradient of 5 mmHg.
Patient 3	Native EFS/ TPV 22 earlier model	No complications occurred during the implant procedure. At the 2-year visit, the subject was found to have a high mean right ventricular outflow tract gradient (37 mmHg) by echocardiography. Close examination by X-ray fluoroscopy and angiography identified occlusion at the lower part of the valve housing. The leaflets of the TPV were normal. At 899 days post-implant, after performing a series of balloon angioplasty procedures, the Melody TPV was implanted. At the 3-year visit, echocardiography indicated a high mean right ventricular outflow tract gradient (42 mmHg) but no pulmonary regurgitation. At 1,458 days post-index procedure, the subject underwent reintervention and received 3 balloon-expandable bare metal stents and a Melody TPV. At the 5-year visit, echocardiography detected no pulmonary regurgitation, with a mean right ventricular outflow tract gradient of 4 mmHg.
Patient 4	Harmony TPV/ cTPV 25 (predecessor model)	Implant was challenging in this subject. cTPV 25 was implanted at the intended position, but backfolding was observed at both proximal and distal ends. Balloon dilatation was performed immediately after implantation to optimize valve function. At the 1-year visit, there was no evidence of device embolization, migration, or stent fracture; however, mild pulmonary regurgitation was noted.

	Study/device	Summary
Patient 5	Harmony TPV/ cTPV 25 (predecessor model)	Due to the anatomy of the subject, the valve was implanted at a position extremely distal to the intended area, causing infolding of struts in the inflow end. After several attempts to dilate the balloon were made to resolve infolding, a stent was placed within the Harmony TPV. Then Melody TPV was implanted within the Harmony TPV. At the 1-year visit, there was no evidence of device embolization, migration, or stent fracture. No paravalvular leak or pulmonary regurgitation was present.
Patient 6	Harmony TPV/ cTPV 25 (predecessor model)	No complications occurred during the implant procedure. The subject started complaining of chest pain at 1 day post-procedure. The subject underwent reintervention at 23 days post-procedure. The Harmony TPV frame was found to be partially out of alignment toward the inside, creating a stenosis over the entire right ventricular outflow tract. Therefore, a stent was placed and then a 26-mm Edwards SAPIEN S3 transcatheter heart valve was implanted. At the 6-month visit, there was no evidence of device embolization, migration, or stent fracture. No pulmonary regurgitation or paravalvular leak was present.

6.B Outline of the review conducted by PMDA

6.B.(1) Appropriateness of using submitted clinical study results for evaluation

6.B.(1).1) Applicability of data to the Japanese population

Only a limited number of Japanese patients participated in the clinical study. PMDA therefore asked the applicant to explain whether the clinical study results are applicable to the Japanese population.

The applicant's explanation:

For the reasons listed below, the applicant considers that there is almost no difference between the intended patient populations of the Harmony TPV System in Japan and the US in terms of patient characteristics, medical service environment, and ethnic difference, and that even if there is a difference, it is unlikely to affect efficacy or safety. The clinical study results can therefore be used to evaluate the efficacy and safety of the Harmony TPV System.

(1) The intended patient population of the Harmony TPV System is patients with severe pulmonary regurgitation who previously underwent surgical repair (patch repair) or transcatheter intervention (balloon valvuloplasty) for the right ventricular outflow tract and clinically need pulmonary valve replacement. The baseline characteristics (e.g., underlying diseases) and treatment plan (e.g., timing of intervention) in such patients do not differ between Japan and the US.

(2) One of the differences between the US and Japan in terms of lesions to be treated is the difference in previous patch repair. As has been shown in the Native EFS study and Harmony TPV study, implant of the Harmony TPV System can be considered regardless of the materials used in the previous patch repair.

(3) One of the differences in treatment procedure between the US and Japan is that in the US, more devices for transcatheter pulmonary valve implantation are available, such as the Melody TPV, which has not been approved in Japan, and therefore, physicians in the US are

likely to be more familiar with the procedures. In contrast, there is less experience in transcatheter pulmonary valve implantation in Japan. However, product training is provided to physicians of study centers participating in the Harmony TPV study both in and outside Japan before they perform the treatment procedure. After the market launch, the applicant plans to provide similar training to physicians before they perform the treatment procedure; therefore, the difference is not considered significant.

(4) In the Harmony TPV study, no unique patient characteristics have been identified in the Japanese population although only 2 Japanese subjects underwent implant (Table 13). The prevalence of congenital heart disease in adults does not differ between Japan and other countries. Therefore, the results of the Harmony TPV study can be applied to the Japanese patient population. Both Japanese subjects completed the 1-year follow-up visit with favorable hemodynamics (mean right ventricular outflow tract gradient <15 mmHg; minor or lower degree of pulmonary regurgitation; absence of paravalvular leak). Neither subject had needed catheterization or surgical intervention during the follow-up period. One of the subjects had a brachial plexus injury due to positioning of the arm during the procedure, and the event resolved in response to physical therapy.

Table 13. Characteristics of Japanese patients

	Patient 1	Patient 2
Sex	Female	Female
Age (years)	[redacted]	[redacted]
Body weight (kg)	59.3	45.0
Original diagnosis	DORV	Tetralogy of Fallot (with pulmonary atresia)
Type of surgical patch materials	Autologous pericardium	Equine pericardium
Number of previous open heart surgeries	2	2

PMDA's view:

Although the applicant's explanation is generally acceptable, the difference in patch repair method should be taken into account. While valved patches are commonly used in Japan, they are rarely used in other countries. The difference in the patch repair method will not cause problems in evaluation if patients not suitable for Harmony TPV implant (i.e., those with a stenosed valve and the stenosis cannot be eliminated) are excluded [see Section "6.B.(4).3).(a) Applicable patches"].

Currently, there are no transcatheter pulmonary valves approved in Japan for treatment of patients who previously underwent patch repair or balloon valvuloplasty. Given this situation, ideally, a larger number of Japanese patients should have been included in the clinical studies in order to evaluate whether the trend in the study results of the Japanese population is consistent with that in the overall population. Nevertheless, there seem to be only small ethnic differences in the anatomy of the right ventricular outflow tract, pathological condition, etc. In addition, there were

no concerns regarding the implant procedure in the Japanese subjects. Therefore, taking into account the comments from the Expert Discussion, PMDA concluded that the results from the clinical studies can be used to evaluate the efficacy and safety of the Harmony TPV System in Japanese patients provided that adequate post-marketing safety activities are performed.

6.B.(1).2) Appropriateness of study design

To evaluate the efficacy and safety of the Harmony TPV System based on the submitted clinical study results, PMDA asked the applicant to explain the following:

(1) The appropriateness of the primary efficacy endpoint (i.e., percentage of subjects with acceptable hemodynamic function at 6 months) and of the performance target of 75% for the endpoint.
(2) The appropriateness of using descriptive statistics for the analysis.

The applicant's explanation:

(1) The appropriateness of the primary efficacy endpoint and performance target

The objective of the treatment of patients with severe pulmonary regurgitation, the intended patient population of the Harmony TPV System, is to eliminate pulmonary regurgitation without compromising the hemodynamics of forward flow; therefore, hemodynamic function was selected as the primary efficacy endpoint. In addition, clinical data collected in the Native EFS study, a feasibility study of the Harmony TPV System, showed that the hemodynamic performance at 6 months was very consistent with that at 12 months, as with bioprosthetic valves used in other areas. Therefore, hemodynamics that have stabilized after valve implant can be assessed by evaluating data at 6 months.

The performance target of 75% was selected based on the 2 studies that evaluated transcatheter pulmonary valve implantation in the right ventricle-to-pulmonary artery conduit (Melody study and COMPASSION S3 study). The Melody study was a post-marketing clinical study of the Melody TPV, and its primary endpoint was "acceptable hemodynamic function and freedom from reintervention at 6 months post-implant" (which is similar to the endpoints of the Native EFS and Harmony TPV studies), with the performance target of 75%. There is a difference in the cut-off value for the mean pressure gradient criteria: 30 mmHg in the Melody TPV study and 40 mmHg in the Harmony TPV study. The COMPASSION S3 study was a study of the SAPIEN 3 Transcatheter Heart Valve, which is implanted in the pulmonary valve position. The study used a similar primary endpoint to evaluate TPV dysfunction at 1 year post-implant, with the performance target of 25% failure (equivalent to the performance target of 75% success). As with the Melody TPV and SAPIEN 3 Transcatheter Heart Valve, the Harmony TPV System was designed to provide a less invasive option to restore the pulmonary valve function of patients with

congenital heart disease. The Harmony TPV System differs from the other 2 products in that the intended patients are those who previously underwent patch repair or transcatheter intervention (balloon valvuloplasty). Despite the difference, it is reasonable to select a success criterion for the Harmony TPV System that is similar to those of other transcatheter TPV devices, because the Harmony TPV System has potential benefits similar to those of other transcatheter TPV devices—namely, reducing the number of surgeries in the lifetime of a patient.

(2) The appropriateness of using descriptive statistics for the analysis

Patients with congenital heart disease are relatively rare (approximately 1% of the population). Approximately 20% of patients with congenital heart disease have right ventricular outflow tract anomalies. Anatomical screening for the Harmony TPV System further limits patients eligible for the use of the device. Because of such circumstances, a clinical study to test hypothesis was expected to require a very long period of patient enrollment. Given the needs for low invasive transcatheter pulmonary valve treatment for the intended patient population of the Harmony TPV System and the feasibility of development of the device, it is appropriate to perform analyses by descriptive statistics.

PMDA's view:

The basic performance of the prosthetic valve, namely, the presence/absence of stenosis and regurgitation, should be evaluated to assess the efficacy. Since the results of the Native EFS study indicated no major change in hemodynamics after 6 months, the applicant's view on the primary efficacy endpoint is acceptable. However, given the outcomes of surgery (the standard of care for the intended patients), the performance target for efficacy is not considered to be conservative. Therefore, the study results should be evaluated carefully. PMDA understands the applicant's approach of using descriptive statistics for evaluation because the Harmony TPV System is intended for the treatment of a rare disease and only a small number of patients are eligible for the device due to anatomical requirements, and also taking into account the clinical need for the device and the feasibility of its development.

Based on the above review as well as comments from the Expert Discussion, PMDA concluded that it was acceptable to evaluate the efficacy and safety of the Harmony TPV System in a comprehensive manner based on the submitted clinical study results. However, the results of the clinical studies, for which hypothesis tests were not performed, require careful evaluation. Furthermore, since the Harmony TPV System is a device intended to delay surgery or decrease the total number of surgeries required in the lifetime of the patient, long-term data including durability are important for evaluating the risks and benefits of the Harmony TPV System.

6.B.(2) Efficacy and safety of Harmony TPV System

PMDA's view:

Even though the primary efficacy endpoint exceeded the performance target, the study results should be evaluated carefully for the following reasons: (a) the performance target is not considered to be conservative; (b) the primary efficacy endpoint is analyzed in the Implanted >24 Hours Cohort; and (c) the percentage of subjects with acceptable hemodynamic function at 6 months was 89.2%. In addition, the long-term data of the Harmony TPV System showed that freedom from device failure in the Attempted Implant Cohort was 82.8% at 1 year post-implant and 69.4% at 5 years post-implant. PMDA therefore asked the applicant to explain in more detail the efficacy of the Harmony TPV System as compared with the outcomes of conventional surgical procedures.

The applicant's explanation:

Only 17 subjects in the Native EFS study (feasibility study) have completed the 5-year follow-up. Follow-up data collected in the Native EFS study and Harmony TPV study cover a far shorter period of time than the long-term follow-up data reported for many surgical therapies. This precludes a thorough comparison between the results of the Harmony TPV System and the long-term results of surgery, the conventional treatment option.

The reported outcomes of conventional surgical procedures, namely, freedom from reintervention at 10 years are as follows: 76.1%–93.1%,[6,7] for expanded polytetrafluoroethylene (ePTFE) valved patches or ePTFE valved extracardiac conduit; 74%[8] for Freestyle stentless xenografts, 69%–88%[9,10] for homografts, 75%–89%[11,12] for bioprosthetic valves with stent; and 75%–79%[10, 13] for Contegra conduit. On the other hand, these results are affected by patient characteristics and variations in product size. For instance, the younger the age at surgery (i.e., the smaller the conduit size), the higher the risk of early reintervention becomes.

Among device failures of the Harmony TPV System, implant procedure-related events occurred mainly with cTPV 25 (predecessor model). Freedom from device failure was 90% at 1 year in subjects in whom implantation of the TPV 22 earlier model, cTPV 22 (predecessor model), or mTPV 25 (proposed device) was attempted. The Kaplan-Meier estimate for freedom from stent fracture was 80.5% at 1 year in subjects implanted with the TPV 22 earlier model or cTPV 22 (predecessor model) for >24 hours, and 100% at 1 year in those implanted with cTPV 25 or mTPV 25 (proposed device). Adverse events associated with stent fracture seldom occurred, and TPV 22 (proposed device) [redacted] the risk of stent fracture has decreased. Therefore, the study results at 1 year are clinically acceptable for the models to be introduced into Japan.

PMDA's view:
Technical success at exit from catheterization lab/operating room was 100% when cTPV 25 was excluded, and no deaths were reported until 30 days post-implant. These findings demonstrate a certain level of efficacy and safety of the Harmony TPV System in relatively early stages after implant. The long-term durability of the Harmony TPV System has been evaluated based on the non-clinical study data and currently available clinical study results, but it has not been adequately established in the clinical setting. The applicant explained that it would gather long-term outcomes after the market launch and, via the instructions for use, would disseminate cautionary statements and the long-term results from the clinical studies. PMDA considers the applicant's actions are acceptable. Taking account of the comments from the Expert Discussion, PMDA concluded that the "clinical positioning of the Harmony TPV System" (described below) was important for optimizing the risk-benefit balance.

6.B.(3) Clinical positioning of Harmony TPV System

The applicant's explanation about the clinical positioning of the Harmony TPV System:
It is difficult to accurately compare the outcome data of the Harmony TPV System with those of surgery. However, because of its low incidence of procedure-related complications and shorter length of hospital stay, the risk-benefit profile of the Harmony TPV System may be more favorable than that of surgery. Therefore, transcatheter treatment with the Harmony TPV System should be considered in cases where surgery is not judged as the best option by a medical team with sufficient knowledge and experience in the treatment of congenital heart diseases.

PMDA's view on the clinical positioning of the Harmony TPV System:
The risk-benefit balance of the Harmony TPV System should be optimized based on the discussions in the following sections 6.B.(3).1) Outcomes of surgical procedures in Japan and 6.B.(3).2) Potential risks associated with Harmony TPV System.

6.B.(3).1) Outcomes of surgical procedures in Japan

According to the FY 2017 annual report by the Japanese Association for Thoracic Surgery, outcomes of surgical procedures are as follows[14]: mortality at 30 days post-surgery in patients who underwent right ventricular outflow tract repair/reconstruction was 0.3% (2 of 583 patients), mortality at 30 days post-surgery in patients who underwent pulmonary artery repair/reconstruction including reoperation was 1.5% (6 of 406 patients).

The report of a retrospective study[15] of right ventricular outflow tract reconstruction with an

ePTFE valved extracardiac conduit (a frequently performed surgical procedure in Japan) contains the outcomes of the surgical procedure in 1,776 patients at 65 hospitals in Japan from 2001 to 2020. The report includes overall results of patients who received a valved conduit of 8 to 24 mm (median follow-up period, 3.3 years) and Kaplan-Meier estimates at 5 and 10 years in 668 patients (mean age 14.3 ± 9.9 years, body weight 41.1kg ± 16.5kg) who received a valved conduit of 20 to 24 mm, similar size to that of the Harmony TPV. The overall survival was 98.0% (199 at risk) at 5 years post-surgery and 95.7% (48 at risk) at 10 years post-surgery. The rate of freedom from reintervention was 96.4% (191 at risk) at 5 years post-surgery and 87.4% (42 at risk) at 10 years post-surgery. The rate of freedom from reoperation was 98.0% (193 at risk) at 5 years post-surgery and 90.5% (45 at risk) at 10 years post-surgery.

6.B.(3).2) Potential risks associated with Harmony TPV System

The Harmony TPV System is a transcatheter device for pulmonary valve replacement and anatomical requirements vary substantially between patients. Therefore, it may not always be possible to perform implantation in an optimal manner. This, together with the clinical study results submitted by the applicant, raises concerns about risks such as re-replacement in an early stage or several years after implantation, regurgitation, and paravalvular leak. In addition, the device is to be implanted in a wide area covering the right ventricular outflow tract to the pulmonary artery bifurcation. In view of the size and shape of the Harmony TPV, adhesion may occur long after implantation. Subsequent surgical reconstruction may be associated with substantial risk and difficulties because homografts are not readily available in Japan. Furthermore, there is also a concern about durability due to the paucity of data for assessing long-term efficacy and safety.

The applicant explained that the Harmony TPV System had the benefit of avoiding reoperations for a certain period of time. However, this benefit has not been clearly demonstrated, in view of the currently available clinical study results and the fact that reoperation risk increases after Harmony TPV implant. Nevertheless, the risks and benefits of the Harmony TPV System can be properly balanced as long as it is used in patients who are ineligible for conventional surgical treatment but eligible for Harmony TPV, because in Japan there are no transcatheter pulmonary valves that can used in such patients. A medical team including cardiac surgeons should determine patient eligibility for treatment with the Harmony TPV System by thoroughly considering patient characteristics, age at implantation, anatomical requirements, cardiac function, comorbidities, and other risks, and should provide the treatment only to patients who can respond to the treatment effectively and safely.

The population of the submitted clinical study results is not limited to patients ineligible for surgical procedures. Whether a patient is ineligible for surgery is decided based on not only anatomical requirements and age but also comprehensive consideration of various factors, as mentioned above. Therefore it is difficult to retrospectively extract patients eligible for the Harmony TPV System (i.e., those who have no effective and safe treatment options other than the Harmony TPV system) from the subjects participating in the submitted clinical studies.

Taking account of comments raised in the Expert Discussion and based on the clinical study results, PMDA concluded that the Harmony TPV System can be used only in patients who have no effective and safe treatment options other than the Harmony TPV system, for the following reasons:

(1) The submitted clinical study results show a certain level of efficacy and safety of Harmony TPV as a prosthetic valve.

(2) No other transcatheter prosthetic valves have been approved that are intended to be used in the same patient population as that of the Harmony TPV System.

In addition, based on the long-term data of the clinical studies submitted and information including use-results survey data, PMDA considers that it is important to examine the safety and efficacy of the Harmony TPV System as well as long-term data including durability in the intended patients in Japan after the market launch, and to take risk minimization actions as necessary. PMDA therefore decided to impose approval conditions.

6.B.(4) Risk minimization measures

PMDA reviewed actions to be taken to minimize the risks identified in the clinical study results (see the following sections).

6.B.(4).1) TPV 22

During the follow-up period of the clinical studies, 21 subjects had a mean pressure gradient of >20 mmHg, and 18 of them were implanted with TPV 22 (TPV 22 earlier model or cTPV 22 [predecessor model]). Since it has been suggested that the smaller the valve size, the larger the pressure gradient becomes, PMDA asked the applicant to explain the details of the risk analysis.

The applicant's explanation:

In most of the patients, the mean pressure gradient in the follow-up period was higher than pre-implant levels, as a consequence of treatment of severe pulmonary regurgitation, but this finding was rather predictable, according to the physicians performing implantation. The mean pressure gradient was relatively stable throughout the follow-up period and TPV function was not impaired

even at >20 mmHg, suggesting that mean pressure gradient does not always serve as an indicator for the necessity of reintervention.

The mean pressure gradient in the Pooled Analysis Cohort (N = 70) at 6 months was 14.0 ± 5.3 mmHg, which is favorable pressure gradient expected in subjects implanted with Harmony TPV, according to the physicians performing implantation in the Native EFS study and Harmony TPV study. While mean pressure gradient is an important evaluation parameter in the follow-up of patients, it is not known if this alone serves an indicator for reintervention. Currently, the risk of potential harm caused by a moderate to severe pressure gradient has been limited to a reasonably low level, and the residual risk is deemed acceptable compared with the therapeutic benefits.

PMDA's view:
Subjects implanted with TPV 22 frequently had a mean pressure gradient of >20 mmHg, and the applicant explained that clinical risks associated with the finding are acceptable. The applicant's explanation is reasonable to some degree, but a residual pressure gradient is associated with smaller valve size also in conventional transcatheter prosthetic valves. At present, there is no evidence supporting that the pressure gradient at the pulmonary valve position alone serves as the indicator for reintervention. However, the increased pressure gradient may become a potential risk, and pressure gradient is one of the important factors that necessitate close monitoring during follow-up. Therefore, information on the outcomes (e.g., pressure gradient and regurgitation) by size (TPV 22 or TPV 25) should be provided via the instructions for use or other materials. Based on the applicable diameter of TPV 22 or TPV 25 (anatomical size), both sizes may become options for a single patient depending on their anatomy. Accordingly, PMDA instructed the applicant to provide cautionary statements in the instructions for use etc. to the effect that the valve size should be selected only after considering factors such as the degree of compression against the right ventricular outflow tract/pulmonary artery and post-implant pressure gradient, in addition to the patient's anatomy. The applicant agreed.

6.B.(4).2) Access site

In the clinical studies, the femoral vein (67 subjects) or internal jugular vein (4 subjects) was selected as the venous access site for the Harmony TPV System. PMDA asked the applicant to explain the reason for selecting the internal jugular vein, and the details of the risk analysis for each access route.

The applicant's explanation:
Access via the internal jugular vein was selected because of femoral vein occlusion in these subjects. Of the 4 subjects who underwent internal jugular vein access, 2 experienced procedure-

related adverse events (other infection associated with peripherally inserted central venous catheter, brachial plexus injury), which were unrelated to access sites. Establishing venous access to the femoral vein or internal jugular vein is considered a standard procedure of cardiovascular intervention. The applicant recommends femoral vein access, based on the data evaluated in the design and clinical studies of the Harmony TPV System. However, the instructions for use will include cautionary statements regarding access site selection to the following effect:

> If the femoral vein difficult to use, such as due to femoral vein occlusion, internal jugular vein access should be considered.

In addition, the post-marketing training program will also cover topics regarding access route of the Harmony TPV System.

PMDA's view:

PMDA understands the applicant's explanation about the necessity of selecting the internal jugular vein in case of femoral vein occlusion or other cases. In the clinical studies, no particular access site-related problems occurred, although this finding was from a small sample size. Therefore, the applicant's plan to provide cautionary statements in the instructions for use and to provide training program to ensure safety is acceptable. The applicant should gather information on access sites through a use-results survey and take additional risk minimization actions, such as updating the content of training, as necessary.

6.B.(4).3) Previously performed surgical repair

6.B.(4).3).(a) Applicable patches

The Harmony TPV System are expected to be used in patients who previously underwent patch repair. Since various types of patches are available, PMDA asked the applicant whether the characteristics of the previously implanted patch (e.g., the type of patch or patch area size) should be considered before using the Harmony TPV System.

The applicant's explanation:

The Harmony TPV System is intended to be implanted in the right ventricular outflow tract regardless of the patch materials used in surgical repair. The results of the Native EFS study and Harmony TPV study did not indicate evidence that the subject's outcome was affected by the raw materials of the patch. No data on the patch area were collected in the clinical studies. However, since a patch is lined with endocardium or endothelium, the coefficient of friction probably does not differ significantly between a patch lined with endothelium and the pulmonary artery lined with endothelium. Therefore, the patch area is unlikely to affect the patient's clinical outcome.

PMDA's view:

PMDA understands the applicant's explanation that the raw material or area of the patch does not affect the clinical outcome. In other countries, autologous pericardium, xenograft pericardium, and ePTFE patches without a valve are mainly used in patch repair. In contrast, valved ePTFE patches are commonly used in Japan, and a valve may be placed when an autologous pericardium patch is used; therefore, an additional risk analysis of this difference should be performed. Due to the difference in the patch repair methods, Japanese patients (previously undergoing patch repair) who are eligible for the Harmony TPV System may have a valve left in the pulmonary valve position and therefore may more often have both pulmonary regurgitation and stenosis than patients in the US. In the clinical studies, only data on patch materials were collected for the case reports; therefore, precise information was not available on patients who had received a valved patch.

In patients with a valved patch or a native valve that is stenosed, if the stenosed valve is immobilized due to calcification or other factors and the stenosis cannot be eliminated, the Harmony TPV System may not be accurately placed and deployed. When using the Harmony TPV System, it is important to ensure that stenosis has been eliminated in patients with the stenosed valve so that it does not inhibit implantation of the Harmony TPV. PMDA instructed the applicant to provide cautionary statements to this effect in the instructions for use or other materials. The applicant agreed.

6.B.(4).3).(b) Other surgical repair

In the proposed intended use of the Harmony TPV System, only patch repair was mentioned as "the previously performed surgical repair of the right ventricular outflow tract." PMDA asked the applicant to explain whether the Harmony TPV System should be indicated also for patients who previously underwent surgical valvotomy to treat pulmonary stenosis, for example.

The applicant's explanation:

The proposed intended use mentioned only "patch repair" as surgical repair. However, there is no anatomically distinguishable difference between balloon valvuloplasty and surgical valvotomy/commissurotomy in terms of consideration of eligibility. Therefore, patients previously undergoing surgical valvotomy/commissurotomy can become candidates for Harmony TPV implant if they have appropriate anatomical structures. In the Harmony TPV study (pivotal study), 2 subjects with pulmonary stenosis had previously undergone valvotomy. There is no clear difference in outcomes between the subjects previously undergoing valvotomy and those previously undergoing balloon valvuloplasty, and the subjects previously undergoing valvotomy were eligible at screening. This supports that the Harmony TPV System can be used also in such subjects. In the US, the Harmony TPV System is approved and its indication is not limited to

patients who previously underwent patch repair. In Japan, probably a certain number of patients have undergone surgical valvotomy/commissurotomy, in addition to those previously undergoing patch repair. Therefore, the applicant will modify the wording of Intended Use to ensure that "surgical repair" is not limited to patch repair.

PMDA accepted the applicant's explanation.

6.B.(4).4) Anatomical requirements

The applicant's explanation about the intended patient population:

The majority of the intended patients are expected to have a medical history of tetralogy of Fallot, but patients with the following conditions may become eligible if they meet the criteria such as intended use, anatomical requirements, etc.:

> Other congenital heart disease (e.g., truncus arteriosus persistent, pulmonary artery atresia with ventricular septum defect, complete transposition of the great vessels, corrected transposition of great vessels, double outlet right ventricle, pulmonary atresia with intact ventricular septum, and Noonan syndrome) and pulmonary stenosis.

The following will be performed to clarify anatomical requirements for patient screening:

(a) Requirements for TPV size will be specified in the instructions for use.
(b) After the market launch, Medtronic Japan Co., Ltd. will support physicians by providing them with recommendations on how to select the device to be used, as it did in the clinical studies.

PMDA's view:

As the applicant explained, it is difficult to exhaustively define individual underlying conditions and previously performed surgical techniques that meet eligibility requirements for treatment with Harmony TPV System. However, since the anatomies of the intended patient population of the Harmony TPV System (i.e., those with congenital heart disease with right ventricular outflow tract anomalies) vary enormously, pre-procedure screening for anatomical requirements must be performed properly to ensure the efficacy and safety of the device. On the basis of the comments raised in the Expert Discussion, PMDA instructed the applicant to disseminate (a) the following cautionary statements and (b) anatomical requirements presented by the applicant, through the instructions for use and other materials, and the applicant agreed:

- Implantation of the Harmony TPV in patients with short main pulmonary artery may cause branch pulmonary artery stenosis; therefore, careful assessment is required (e.g., in patients who previously underwent an REV procedure, which is a surgical procedure to reconstruct the right ventricular outflow tract using autologous tissue).

- In some patients, the conduction system may run in the right ventricular outflow tract as a result of the surgical technique selected for original diagnosis. Such patients are at risk of arrhythmia after implantation. This risk should be carefully assessed taking account of pretreatment (for example, patients with corrected transposition of great vessels who did not undergo the double switch procedure).
- Patients with pulmonary regurgitation (the intended patient population of the Harmony TPV System) may have stenotic lesions in addition to regurgitant lesions. In order to ensure safe implantation of the Harmony TPV System, patients should be checked to confirm the absence of subvalvular stenosis, supravalvular stenosis, and bifurcation stenosis as well as stenosis at valve position.

It is important to appropriately select eligible patients for treatment with the Harmony TPV System (patients are eligible if the device offers the optimal treatment for them), taking into account of anatomical requirements and their eligibility for surgery. PMDA asked the applicant to ensure that eligible patients are selected appropriately. The applicant explained it would ensure the following:

(a) After the introduction of the Harmony TPV System in Japan, patient screening will be mandatory for a specified period of time;
(b) A screening committee including a proctor physician, pediatric cardiologist, and cardiovascular surgeon will be established. The committee will independently assess patient eligibility.

PMDA considered that the applicant's proposal is reasonable and accepted.

6.B.(4).5) Post-implant antithrombotic therapy

The Japanese protocol of the Harmony TPV study (pivotal study) recommended prescribing aspirin (75–100 mg) and anticoagulant therapy (warfarin) for 3 months post-implant based on the "Guidelines for Surgical and Interventional Treatment of Valvular Heart Disease (2012 revised edition)" by the Japanese Circulation Society. However, the percentage of patients who received antithrombotic regimens in the Harmony TPV study was as follows: antiplatelet therapy 75% and anticoagulant therapy 2.1% at discharge, and antiplatelet therapy 83.3% and anticoagulant therapy 2.1% at 6 months post-implant. PMDA asked the applicant to explain appropriate antithrombotic therapy post-implant after the market launch.

The applicant's explanation:

No medication standards have been established in Japan. Taking into account of findings from the clinical studies, it is more appropriate to recommend antiplatelet therapy (e.g., aspirin) according

to the hospital policy or at the discretion of the physician, rather than anticoagulant therapy.

PMDA's view:
The applicant's proposal is reasonable, for the following reasons:

(a) Since no medication standards have been established in Japan, antithrombotic therapy should be determined taking into account the risks of blood clots and bleeding in individual patients.
(b) No blood clot or bleeding events causing problems were reported in the clinical studies of the Harmony TPV System.

The applicant should thoroughly investigate how antithrombotic therapy is used in clinical practice and associated adverse events through the use-results survey, which will be discussed later, to reduce the risks.

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

The applicant's explanation about the post-marketing safety activities for the Harmony TPV System:
Prior to performing treatment with the Harmony TPV System, physicians are required to complete a training program given by the applicant. The training program has comprehensive content based on the experience gained in the clinical studies. Operating physicians are required to perform procedures in at least 3 patients under the supervision of a proctor physician. In addition, as discussed above, after introduction of the Harmony TPV System in Japan, patient screening is required for a specified period of time. A screening committee including a proctor physician, pediatric cardiologist, and cardiovascular surgeon will be established so that it can determine patient eligibility independently. Furthermore, in cooperation with the Transcatheter Heart Valve Therapy Association, the applicant with prepare appropriate use criteria that include the criteria for the medical institutions, operators, and eligibility.

PMDA's view:
Since only a few Japanese patients participated in the clinical study, technical support should be provided by proctor physicians versed in the treatment with the Harmony TPV System. In order to optimize the risk-benefit balance of the Harmony TPV System, it is most critical to ensure that physicians who know well the characteristics of treatment with the device appropriately determine patient eligibility for the device after considering conventional therapy options, such as surgical procedures. Further, appropriate actions should be taken in case of complications associated with the Harmony TPV System and placement procedures. Therefore, treatment with the Harmony TPV System should be performed by physicians who can provide suitable treatment with sufficient experience in medical treatment and surgical procedures for patients with congenital

heart disease at medical institutions with such experience and ability. The proper use criteria will be prepared in cooperation with relevant academic societies, and patient eligibility will be assessed by the screening committee; PMDA therefore accepts the applicant's explanation because it is appropriate.

Based on the above, PMDA considered that it is appropriate to impose approval conditions regarding the requirements for medical institutions, operators, and eligible patient selection.

6.B.(6) Intended use

Based on the above discussion, PMDA concluded that the intended use should be as follows to clarify the intended patient population:

Intended use or indication

The Harmony Transcatheter Pulmonary Valve Replacement System is used in patients with severe pulmonary regurgitation who previously underwent surgical repair or transcatheter intervention (balloon valvuloplasty) for the right ventricular outflow tract and clinically need pulmonary valve replacement. However, such patients are eligible only if they cannot undergo surgery and the Harmony Transcatheter Pulmonary Valve Replacement System is considered to offer the optimal treatment for them. Patients who have a right ventricle-to-pulmonary artery conduit or a prosthetic valve are not eligible for treatment with the Harmony Transcatheter Pulmonary Valve Replacement System.

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

7.A Summary of the data submitted

Table 14 shows the summary of the use-results survey (draft) presented by the applicant for the present application. Since the intended patient population in Japan for the Harmony TPV System is expected to be small, all patients will be registered during the registration period. In the clinical studies, some patients underwent re-intervention within 5 years post-implant, and therefore the durability of the Harmony TPV System should be evaluated also by the use-results survey. Thus the observation period was defined as 5 years post-implant.

Table 14. Summary of use-results survey (draft)

Item	Detail
Population	Patients with severe pulmonary regurgitation who are eligible for the Harmony TPV System
Planned sample size	All patients who are registered during the registration period
Rationale	Since only a few patients are expected to be treated with the Harmony TPV System, the survey covers all patients during the registration period. A patient registration period of 2

Item	Detail
	years post-approval was selected. An observation period of 5 years was selected to evaluate the durability of the device.
Survey period	7 years and 6 months (marketing preparation period and patient registration period, 2 years post-approval; observation period, 5 years; analysis period, 6 months)
Key survey items	• Percentage of subjects with acceptable hemodynamic function and freedom from reintervention (6 months post-implant) • Procedural success rate (30 days post-implant) • All-cause death, reoperation, reintervention, valve dysfunction, procedure- or device-related serious adverse events (5 years post-implant)

7.B Outline of the review conducted by PMDA

PMDA concluded that the applicant should collect data from all patients in whom the Harmony TPV System has been used to evaluate its safety and efficacy and examine the eligibility of patients implanted with the device, and should take additional risk minimization actions as necessary, for the following reasons:

- The Harmony TPV System will be the first approved transcatheter prosthetic valve in Japan for patients with severe pulmonary regurgitation who previously underwent surgical repair or transcatheter intervention (balloon valvuloplasty) for the right ventricular outflow tract and clinically need pulmonary valve replacement.
- Only 2 Japanese subjects participated in the clinical study. There are only scarce clinical data (e.g., long-term outcomes, the patient characteristics, and anatomical features) in the intended Japanese patient population for the Harmony TPV System.

PMDA concluded that the applicant's plan for the use-results survey is appropriate and decided to include the use-results survey as an approval condition.

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

8.A Summary of the data submitted

The applicant submitted Instruction for Use (draft) as an attachment in accordance with the Notification titled "Application for Marketing Approval of Medical Devices" (PFSB Notification No. 1120-5, dated November 20, 2014).

8.B Outline of the review conducted by PMDA

On the basis of the conclusion of the Expert Discussion, as described earlier in Section "6.B. Outline of the review conducted by PMDA," PMDA concluded that there were no particular problems with the proposed Instruction for Use, provided that the applicant advises necessary

caution.

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

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

The new medical device application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of 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

When conducting the review, PMDA primarily focused on (1) the clinical positioning of the Harmony TPV System; (2) the efficacy and safety of the device; and (3) post-marketing safety activities. PMDA reached the following conclusions, taking account of deliberations at the Expert Discussion:

(1) Clinical positioning of the Harmony TPV System

The outcomes of surgical procedures, including long-term outcomes, are favorable in Japan. On the other hand, in the Native EFS study (feasibility study) and Harmony TPV study (pivotal study), a certain proportion of patients implanted with the Harmony TPV did not show improved hemodynamic function, and there are no clear long-term data of the Harmony TPV System. In addition, there are substantial risks associated with reoperation after Harmony TPV implant. Based on the above, currently, the Harmony TPV System should be positioned as a new treatment option for patients who cannot undergo surgery with no other effective therapies available.

(2) Efficacy and safety of the Harmony TPV System

Currently available study data show that some patients required reintervention after Harmony TPV implant and other patients had valve dysfunction. Patients who cannot undergo surgery have a poor prognosis, and they are the intended patient population for the Harmony TPV System. This raises concern over the long-term outcomes after the Harmony TPV transplant. However, PMDA concluded that the Harmony TPV System has clinically acceptable efficacy and safety in this patient population provided that post-marketing safety activities are adequately implemented.

(3) Post-marketing safety activities

The Harmony TPV System can improve pulmonary regurgitation less invasively than surgery, but the risk of unsuccessful procedure and associated complications cannot be avoided completely. In order to keep a favorable risk-benefit balance of the Harmony TPV System, it is most critical to ensure that physicians appropriately determine patient eligibility for the device after (a) fully understanding the characteristics of treatment with the device appropriately and mastering techniques required through a training program etc. and (b) considering conventional therapy options, such as surgical procedures. Therefore, treatment with the Harmony TPV System should be performed by physicians who can provide suitable treatment with sufficient experience in medical treatment and surgical procedures for patients with congenital heart disease at medical institutions with such experience and ability (Approval Conditions 1, 2, and 3).

There is limited clinical experience in transcatheter treatment of pulmonary regurgitation in Japan. Long-term clinical data on the Harmony TPV System are scarce both in Japan and other countries. Accordingly, the applicant should perform the following (Approval Condition 4):

(a) Collect data on the characteristics of intended patient population, procedural success rate, and adverse events from the use-results survey.
(b) Examine the clinical data regarding the Harmony TPV System in view of the post-marketing safety activities discussed above, and take additional risk minimization actions as necessary.

The observation period should be 5 years. The survey period for the use-results survey should be 7 years and 6 months in total (marketing preparation period and patient registration period, 2 years; observation period, 5 years; analysis period, 6 months). Additionally, the applicant should report the long-term data from the clinical studies submitted and assess the long-term outcomes of the Harmony TPV System (Approval Condition 5).

As a result of the above review, PMDA has concluded that the Harmony TPV System may be approved with the following intended use (modified from the proposed text) and approval conditions.

Intended Use

The Harmony Transcatheter Pulmonary Valve Replacement System is used in patients with severe pulmonary regurgitation who previously underwent surgical repair or transcatheter intervention (balloon valvuloplasty) for the right ventricular outflow tract and clinically need pulmonary valve replacement. However, such patients are eligible only if they cannot undergo surgery and the Harmony Transcatheter Pulmonary Valve Replacement System is considered to offer the optimal treatment for them. Patients who have a right ventricle-to-pulmonary artery

conduit or a prosthetic valve are not eligible for treatment with the Harmony Transcatheter Pulmonary Valve Replacement System.

Approval Conditions

1. The applicant is required to take necessary actions in cooperation with the relevant academic societies to ensure that the Harmony Transcatheter Pulmonary Valve Replacement System is used only by medical teams with sufficient knowledge and experience in the treatment of congenital heart disease at medical institutions capable of providing treatment for complications associated with treatment with the Harmony Transcatheter Pulmonary Valve Replacement System.
2. The applicant is required to take necessary actions in cooperation with the relevant academic societies to ensure that the Harmony Transcatheter Pulmonary Valve Replacement System is used, in compliance with the approved indication, by physicians of a medical team satisfying the Approval Condition 1, who have mastered techniques required for manipulating the Harmony Transcatheter Pulmonary Valve Replacement System, have fully learned complications associated with the Harmony TPV procedure, and have acquired other necessary knowledge, by receiving a training program etc.
3. The applicant is required to take necessary actions to ensure that the Harmony Transcatheter Pulmonary Valve Replacement System is used only for eligible patients, in cooperation with the relevant academic societies.
4. The applicant is required to conduct a use-results survey covering all patients treated with the Harmony Transcatheter Pulmonary Valve Replacement System after the market launch, to provide PMDA with the analysis results of long-term outcomes, and to take appropriate actions as necessary.
5. The applicant is required to provide PMDA with the analysis results of the long-term outcomes in participants of the clinical studies submitted for the present application, and to take appropriate actions as necessary.

The product is classified as a biological product. A use-results survey of the product should be conducted. The survey period should be 7 years and 6 months.

PMDA has concluded that the present application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

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