SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Pulmonary valve, prosthesis, percutaneously delivered
Device Trade Name:	Harmony Transcatheter Pulmonary Valve (TPV) System
Device Procode:	NPV
Applicant Name and Address:	Medtronic, Inc. 3576 Unocal Place Santa Rosa, CA 95403
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P200046
Date of FDA Notice of Approval:	March 26, 2021
Breakthrough Device:	Granted breakthrough device status on May 01, 2019 because the device can provide for more effective treatment of a irreversibly debilitating disease; as well represents a breakthrough technology, offers significar advantages over existing approved or cleared alternatives, and is in the best interest of patients.

II. INDICATIONS FOR USE

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.

III. CONTRAINDICATIONS

The Harmony TPV System is contraindicated in patients who have active bacterial endocarditis or other infections or known intolerance to Nitinol (titanium or nickel) or an anticoagulation/antiplatelet regimen.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Harmony TPV system labeling.

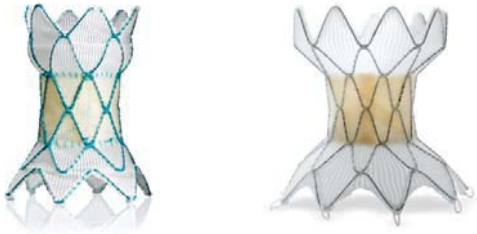
V. DEVICE DESCRIPTION

The Harmony TPV System comprises a TPV and a delivery catheter system (DCS).

Harmony TPV

The Harmony TPV, available in two (2) sizes (TPV 22 and TPV 25), as shown in Figure 1, is composed of self-expanding Nitinol (nickel-titanium alloy) wire struts, a knitted polyester fabric graft, and a porcine pericardial tissue valve, sutured together using polytetrafluoroethylene (PTFE) impregnated polyester suture (TPV 22) or Ultra-high-molecular-weight polyethylene (UHMWPE) suture (TPV 25). The porcine pericardial tissue valve is processed with a proprietary alpha-amino oleic acid (AOA) anti-mineralization treatment.

Figure 1: Harmony Transcatheter Pulmonary Valve

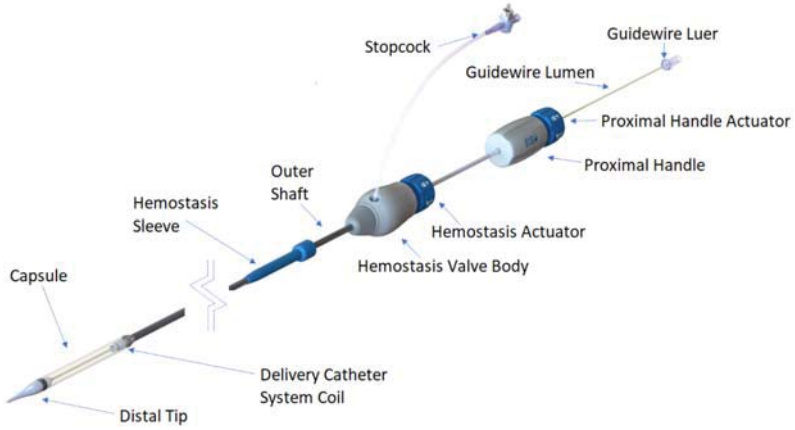


TPV 22 TPV 25

Harmony DCS

The Harmony DCS is a single use, intravascular, over-the-wire delivery catheter incorporating a loading system. The DCS has a 25 Fr crossing profile and is designed to be compatible with commercially available 0.035" intravascular wires. The DCS is available in one model for delivering both the TPV 22 and TPV 25 implants.

Figure 2: Harmony Delivery Catheter System



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of severe pulmonary regurgitation in patients with a native or surgically-repaired right ventricular outflow tract (RVOT), including surgical placement of a right ventricle-pulmonary artery (RV-PA) conduit or a prosthetic valve. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Harmony TPV System has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the Harmony TPV System:

- Death
- Valve dysfunction
- Tissue deterioration
- Hematoma
- Heart failure
- Cerebrovascular incident
- Perforation
- Rupture of the RVOT
- Compression of the aortic root
- Compression of the coronary arteries
- Sepsis
- Pseudoaneurysm
- Erosion
- Stent fracture
- Arrhythmias
- Device embolization or migration
- Pulmonary embolism
- Occlusion of a pulmonary artery
- Laceration or rupture of blood vessels
- Device misorientation or misplacement
- Valve deterioration
- Regurgitation through an incompetent valve
- Physical or chemical implant deterioration
- Paravalvular leak
- Valve dysfunction leading to hemodynamic compromise
- Residual or increasing transvalvular gradients

- Progressive stenosis and obstruction of the implant
- Hemorrhage
- Endocarditis
- Thromboembolism
- Thrombosis
- Thrombus
- Intrinsic and extrinsic calcification
- Bleeding
- Bleeding diathesis due to anticoagulant use
- Fever
- Pain at the catheterization site
- Allergic reaction to contrast agents
- Infection
- Progressive pulmonary hypertension
- Progressive neointimal thickening and peeling
- Leaflet thickening
- Hemolysis

For the specific adverse events that occurred in the clinical study, please see Section X.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Nonclinical laboratory studies on the Harmony TPV System were performed in accordance with *ISO 5840-1:2015, Cardiovascular implants – Cardiac valve prostheses – Part 1: General requirements* and ISO 5840-1:2013, *Cardiovascular implants – Cardiac valve prostheses – Part 3: Heart valve substitutes implanted by transcatheter techniques*.

1. Biocompatibility

Biocompatibility assessments were completed on the Harmony TPV system in accordance with ISO 10993-1:2018, *Biological Evaluation of Medical Devices Part 1: Evaluation and testing within a risk management process*, and the FDA Guidance for Industry and Food and Drug Administration Staff *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process.*" The required testing for each component was determined based on the nature and duration of body contact per ISO 10993-1:2018. Test articles consisted of the patient-contacting device components after exposure to all manufacturing processes, including sterilization. The biocompatibility test results for the Harmony TPV and DCS are summarized in Table 1 and Table 2, respectively.

Table 1: Summary of Harmony TPV Biocompatibility Assessments

Biological Effect per ISO 10993-1	Test Method	Results
Cytotoxicity	ISO MEM elution using L-929 mouse fibroblast cell	Pass
Sensitization	ISO guinea pig maximization sensitization	Pass
Irritation	ISO intracutaneous irritation	Pass
Pyrogenicity	Material mediated rabbit pyrogenicity	Pass
Genotoxicity	Ames bacterial reverse mutation	Pass
	Mouse lymphoma assay	Pass
Implantation	4 weeks - ISO muscle implantation study in rabbit	Pass
	13 weeks - ISO muscle implantation study in rabbits	Pass
Hemocompatibility	*In vitro* hemolysis (indirect)	Pass
	In vitro hemolysis (direct method)	Pass
	Complement activation	Pass
	Thrombogenicity	Pass
Physicochemical	Chemical characterization and toxicological risk assessment	Pass

Table 2: Summary of Harmony DCS Biocompatibility Assessments

Biological Effect per ISO 10993-1	Test Method	Results
Cytotoxicity	ISO elution method	Pass
Sensitization	ISO guinea pig maximization sensitization	Pass
Irritation	ISO intracutaneous irritation	Pass
Acute system toxicity	ISO acute systemic toxicity study in mice	Pass
Pyrogenicity	Material mediated rabbit pyrogenicity	Pass
Hemocompatibility	*In vitro* hemolysis (indirect)	Pass
	In vitro hemolysis (direct method)	Pass
	Complement activation	Pass
	Thrombogenicity	Pass

2. **Bench testing**

A summary of the bench testing results is provided in Table 3.

Table 3: Summary of Harmony TPV System Bench Testing

Test	Purpose	Test Articles	Results
Harmony TPV Testing			
Hydrodynamic testing	To verify hydrodynamic performance including mean pressure gradient and total transvalvular regurgitant fraction against design requirements.	TPV 22 and TPV 25	All valves met the prespecified hydrodynamic performance acceptance criteria.
Leaflet kinematics	To provide qualitative information on the Harmony TPV leaflet function during opening and closing under pulsatile flow conditions.	TPV 22 and TPV 25	All valves were shown to open fully during systole. Full leaflet coaptation with no misalignment, prolapse, or visible leakage path observed during diastole.
Accelerated wear testing with visual inspection	To assess the accelerated wear performance to 200 million cycles.	TPV 22 and TPV 25	All valves survived durability testing to 200 million cycles without functional impairment. At the completion of 200 million cycles, all valves met the prespecified effective orifice area and regurgitation fraction requirements.
Dynamic failure mode	To evaluate potential failure modes associated with structural valve deterioration.	TPV 22 and TPV 25	For characterization only.

Total leakage (transvalvular and paravalvular)	To assess total leakage (transvalvular and paravalvular) of Harmony TPV deployed in a silicone conduit.	TPV 22 and TPV 25	All valves met the prespecified total leakage requirement.
Dynamic regurgitation	To characterize hydrodynamic performance of Harmony TPV over a range of simulated physiological conditions.	TPV 22 and TPV 25	For characterization only.
Visibility	To evaluate the visibility of the Harmony TPV under fluoroscopy.	TPV 25	Implant was visible under fluoroscopy.
Migration resistance	To evaluate the migration resistance of the Harmony TPV.	TPV 22 and TPV 25	All valves met the prespecified acceptance criteria for migration resistance.
Frame fatigue	To demonstrate the fatigue resistance of the valve frame to 600 million cycles	TPV 25	No loss of structural integrity was observed in any of the frames at the completion of 600 million cycles.
Finite element analysis (FEA)	To characterize the structural behavior of the Harmony TPV frame under *in vivo* operational conditions.	TPV 22	For characterization only.
Material fatigue testing	To establish the fatigue strength of the Nitinol frame material at 600 million cycles.	Representative strut from TPV 25	For characterization only.
Probabilistic structural component reliability analysis	To provide a comprehensive assessment of expected structural component reliability.	TPV 22 and TPV 25	For characterization only.
Chronic outward force	To quantify the chronic outward force expected from the Harmony TPV at the maximum and minimum diameters.	TPV 22 and TPV 25	All valves met the prespecified acceptance criteria.

TPV post-deployment dimensional verification	To verify inflow and outflow dimensions post-conditioning satisfy design specifications.	TPV 22 and TPV 25	All valves met the prespecified acceptance criteria.
TPV post-conditioning inspection	To mimic worst-case use condition and account for any potential misloads. The inspection includes verifying no damage to tissue, fabric, suture, and struts of the TPV after worst-case conditioning.	TPV 22 and TPV 25	All valves met the prespecified acceptance criteria. There was no damage to tissue, fabric, suture or struts of the TPV.
TPV post-conditioning dimensional characterization and foreshortening	To characterize device height and diameters at level of each strut, and measure foreshortening of deployed TPV.	TPV 22 and TPV 25	For characterization only.
Frame corrosion	To evaluate corrosion resistance (galvanic, fretting, pitting, nickel ion) of the Harmony TPV frame in accordance with ASTM F 2129	TPV 22 and TPV 25	All valves met the prespecified acceptance criteria.
Magnetic resonance imaging (MRI)	To characterize the compatibility of the Harmony TPV in a magnetic resonance field.	TPV 22 and TPV 25	The device can be safely imaged under the conditions listed in the device labeling.
Glutaraldehyde & isopropyl alcohol (IPA) residuals	To verify glutaraldehyde residuals meet the design requirements and to characterize IPA residual on TPV.	TPV 25	All valves met the prespecified acceptance criteria for glutaraldehyde residuals. IPA residual testing was for characterization purposes only.
Tissue uniaxial strength	To verify the tensile strength of Harmony TPV fixed porcine pericardial tissue meets the minimum Ultimate Tensile Strength (UTS) requirement.	Porcine pericardial tissue	The prespecified minimum UTS requirement for tissue was met.

Flow visualization	To perform a qualitative comparative assessment of flow field characteristics for Harmony TPV by utilizing Particle Image Velocimetry technique.	TPV 22 and TPV 25	All valves exhibited acceptable flow characteristics. The flow exiting the valve in a laminar parallel streamline with minimal vortices observed close to the conduit surface. The peak major Reynold shear stress results were deemed sufficiently low.
Harmony DCS Testing			
Visual inspection	The verify the DCS is free from defects and extraneous matter under magnification.	Harmony DCS	All DCS were free of any defects and extraneous matter.
Dimensional inspection	To ensure the DCS meets the prespecified dimensional specifications.	Harmony DCS	All DCS met the dimensional specifications.
Hemostasis	To ensure the DCS maintains hemostasis.	Harmony DCS	All DCS met the prespecified acceptance criteria for maximum fluid loss.
Tensile testing	To ensure the DCS bonds meet the prespecified tensile strengths.	Harmony DCS	All DCS bonds met the prespecified tensile strength acceptance criteria.
Corrosion resistance	To ensure the DCS is corrosion resistant per ISO 10555-1.	Harmony DCS	All DCS were determined to be corrosion resistant.

Simulated use	To simulate the clinical use of the Harmony DCS, including loading, tracking and deployment of the TPV in a clinically representative 3D track model.	Harmony DCS	All DCS met the prespecified acceptance criteria for simulated use.
Harmony TPV System Design Validation Testing			
Human factors and usability evaluation	To obtain qualitative user feedback for the usability of the user interface and Harmony system interactions.	Harmony TPV 22, Harmony TPV 25, and Harmony DCS	For characterization only.

B. **Animal Studies**

A Good Laboratory Practice (GLP)-compliant chronic animal study was performed to support the safety of the Harmony TPV system. The study evaluated the chronic *in vivo* performance and durability characteristics of the Harmony TPV device compared to the Hancock Porcine Valve Conduit (Model 105). Additionally, the study evaluated the potential for surgical explant ability of the Harmony TPV and the potential for surgical intervention post-explant. A total of 7 test articles and 3 control articles were implanted for 20-24 ± 2 weeks. Table 4 summarizes the chronic animal study results.

Table 4: Harmony TPV System Chronic Animal Study Results

Test/Assessment	Acceptance Criteria	Result
Pathology	• Host tissue growth onto the device making it adherent to the implant anatomy. • No vessel erosion that leads to vessel bleeding or dissection of the pulmonary artery or right ventricle.	Passed. All Harmony TPVs were stably fixed in pace via host tissue adhesions, with no associated vessel bleeding observed.
Thrombogenicity	• Evaluation of the pulmonary angiogram shows embolic event less than or equal to the control group. • Embolization of the stent, graft, suture or valve that leads to downstream clinical events less than or equal to the control group.	Passed. No pulmonary perfusion flow defects or pulmonary emboli were observed.

Test/Assessment	Acceptance Criteria	Result
Hematology	Hemolysis and thrombosis markers better than or equal to the control.	Passed. Results from test and control animals were similar.
Valve function	Harmony TPV pressure gradients and regurgitation/ insufficiency as determined through echocardiographic assessment to be less than or equal to the control group.	Passed. No significant differences were observed for pressure gradient values between the test and control devices at any time point. Further, no regurgitation was observed for test device at any time point, which was equal or better than the control group. There was no sign of right heart dysfunction at necropsy.
Infection	Absence of Harmony TPV infection.	Passed. Cultures obtained from all test and control animals pre-operatively and before termination at week 21 did not yield any microbial growth. In the test group, three of six animals yielded bacterial growth at 10 weeks. Given that other parameters of systemic inflammation (i.e., the WBC count, absolute neutrophil numbers, and fibrinogen levels) were not elevated and well within the normal reference intervals, it was probable that bacterial growth at 10 weeks was attributable to contamination.
Paravalvular/ persistent leaks	No paravalvular leaks with signs of hemolysis, thrombogenicity, and hemodynamics are equal to or better than the control.	Passed. Paravalvular leaks were observed. However, results showed that the Harmony TPV was equal to or better than the control for hemolysis, thrombogenicity, and hemodynamics.
Embolization	No device embolization that causes hemodynamic failure and/or blocks the bifurcation/vessels.	Passed. All Harmony valves were stably fixed in place via host tissue adhesions and no migration of the device was observed.

Test/Assessment	Acceptance Criteria	Result
Stent fractures	No stent fractures that lead to migration, vessel puncture, or stent embolization that blocks off flow or causes impingement of valve.	Passed. Stent fractures did occur, but did not lead to device migration, vessel puncture, stent embolization, or any apparent impingement on valve function.
Surgical explant for potential surgical intervention	Successful removal of the Harmony device and subsequent successful outflow tract repair (i.e., repair can be performed without encountering anomalies that are judged to be initiators of negative clinical outflow tract performance).	Passed.
Loading system	Successful loading of the valve implant into the delivery system.	Passed.
Delivery system	Successful delivery to the target site, deployment of the implant, release of the implant mechanism, and retrieval of the catheter through the implant.	Passed.

C. **Sterilization**

The Harmony TPV undergoes liquid chemical sterilization in a glutaraldehyde solution. The terminal sterilization process involves incubation of the TPV in the sterilant solution at elevated temperatures for a defined period of time. The validated terminal liquid sterilization process has demonstrated a sterility assurance level (SAL) of 10^{-6}.

The Harmony DCS is sterilized via Ethylene Oxide (EtO) in accordance with EN ISO 11135:2014: *Sterilisation of health-care products – Ethylene Oxide –Requirements for development, validation and routine control of a sterilisation process for medical devices*. Residual testing was conducted per ISO 10993-7:2008/Corr 1: 2009: *Biological Evaluation of Medical Devices – Part 7: Ethylene oxide sterilization residuals*. The validated EtO sterilization process has demonstrated a SAL of 10^{-6}.

D. **Packaging and Shelf Life**

The Harmony TPV System components are packaged separately. The TPV component is stored in glutaraldehyde in a glass jar and placed in a protective carton. Evaluations have demonstrated that packaging sterility and performance are maintained after sterilization

and one year real time aging.

The Harmony DCS is placed on a tray and then pouched. The pouched DCSs are then placed in their respective cartons. Evaluations have demonstrated that packaging sterility and integrity are maintained after sterilization and one year accelerated aging.

The shelf life of all components of the Harmony TPV System is one year as demonstrated by packaging integrity and product functional testing on aged samples.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a prospective clinical study to establish a reasonable assurance of safety and effectiveness of transcatheter pulmonary valve replacement with the Harmony TPV System under IDE #G120175. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The clinical study was a prospective, non-randomized, multi-center study and included two phases, i.e., the early feasibility study (EFS) phase and the pivotal study phase. The EFS treated (i.e., catheterized) 21 patients between May 30, 2013 and May 13, 2015 at 3 investigational sites in the U.S. and Canada. The pivotal study treated 50 patients between March 14, 2017 and November 8, 2019 at 13 investigational sites in the U.S., Canada, and Japan. Clinical data from the EFS phase and the pivotal study phase were pooled because largely similar clinical protocols were followed in the two phases.

The study utilized an independent Data Safety Monitoring Board (DSMB), a Clinical Events Committee (CEC), and MRI/echocardiography/explant pathology core laboratories.

1. Key Clinical Inclusion and Exclusion Criteria

Enrollment in the Harmony TPV clinical study was limited to patients who met the following inclusion criteria:

- Patient has pulmonary regurgitation as per one or more of the following criteria:
  - Severe pulmonary regurgitation as measured by continuous-wave Doppler echocardiography, or
  - Pulmonary regurgitant fraction ≥30% as measured by cardiac magnetic resonance imaging
- Clinical indication for surgical placement of a RV-PA conduit or prosthetic pulmonary valve per one or more of the following criteria:
  - Patient is symptomatic secondary to pulmonary insufficiency (e.g., exercise intolerance, fluid overload) as classified by the investigator, or
  - Patient has right ventricular end-diastolic volume index (RVEDVi) ≥150 ml/m^2, or

    - 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

Patients were <u>not</u> permitted to enroll in the Harmony TPV clinical study if they met any of the following 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 (RVOTO) lesions surgically treated with an RV-PA 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 one year
- Planned concomitant implantation of the Harmony TPV in the left heart
- RVOT anatomy or morphology 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

2. Follow-Up Schedule

All patients were scheduled for follow-up examinations at baseline, implant procedure, discharge, 1 month, 6 months, and annually through 5 years. Data collected included demographics and medical history, procedural information, adverse event assessments, transthoracic echocardiography (when available), functional cardiac MRI (when available and not contraindicated), and radiography (fluoroscopy and/or x-ray when available).

3. Clinical Endpoints

The primary safety endpoint was freedom from procedure or device-related mortality at 30-days post implant. The primary effectiveness endpoint was percentage of patients with no Harmony valve reinterventions and acceptable hemodynamic function at 6 months as defined by:

- Mean RVOT gradient ≤40 mmHg as measured by continuous-wave Doppler
    - If a catheterization was performed for clinical purposes, the catheterization peak gradient measurement superseded the continuous-wave Doppler measurement and was used to support the primary effectiveness endpoint. A peak gradient of ≤40 mmHg as measured by catheterization was considered acceptable hemodynamic function

-AND-

- Pulmonary regurgitant fraction <20% as measured by MRI
    - If MRI was contraindicated, a continuous-wave Doppler measurement was used to support the primary effectiveness endpoint. Less than moderate pulmonary regurgitation as measured by continuous-wave Doppler was considered acceptable hemodynamic function.

Only patients implanted >24 hours were included in the analysis cohort of the primary effectiveness endpoint. Both the primary safety and effectiveness endpoints were evaluated descriptively.

Other outcome measures included:

- Technical success at exit from catheterization laboratory/operating room, defined as follows:
    - No device- or procedural-related mortality, with
    - Successful access, delivery and retrieval of the delivery system, and
    - Deployment and correct positioning (including minor repositioning if needed) of the single intended device, and
    - No need for additional unplanned or emergency surgery or reintervention related to the device or access procedure
- Device success out to 5 years, defined as follows:
    - No device- or procedural-related mortality, with
    - Original intended device in place, and
    - 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), and
    - Intended performance of the device, defined as:
        - Structural performance: No migration, embolization, detachment, major stent fracture, hemolysis, thrombosis, endocarditis, and
        - Hemodynamic performance: Relief of insufficiency (pulmonary regurgitation < moderate) without producing the opposite (mean RVOT gradient > 40 mmHg) as measured by continuous wave Doppler, and
    - Absence of para-device complications, as defined by:
        - Paravalvular leak ≥ moderate, or
        - Erosion, or
        - RVOT or pulmonary artery rupture
- Procedural success out to 30 days, defined as follows:
    - Device success at 30 days, and
    - None of the following device- or procedure-related serious adverse events:
        - Life-threatening major bleed
        - Major vascular or cardiac structural complications requiring unplanned reintervention or surgery
        - Stage 2 or 3 acute kidney injury (AKI) (includes new dialysis)
        - Pulmonary embolism
        - Severe heart failure or hypotension requiring intravenous inotrope,

ultrafiltration, or mechanical circulatory support
        - Prolonged intubation >48 hours
- Freedom from TPV dysfunction out to 5 years, defined as follows:
    - RVOT reoperation for device-related reasons
    - Catheter reintervention of the TPV
    - Hemodynamic dysfunction of the TPV (moderate or greater pulmonary regurgitation, and/or a mean RVOT gradient > 40 mmHg)
- Assessment of safety
- Characterization of right ventricular remodeling following TPV implant as assessed via cardiac MR
- Quality of life over time

B. **Accountability of PMA Cohort**

At the time of database lock, a total of 340 patients had enrolled in the clinical study of the Harmony TPV System, 71 of which were catheterized ("Catheterized Cohort") and the remainder were not treated due to various reasons, such as screen failures and enrollment completion. Seventy (70) of the 71 catheterized patients received a Harmony TPV implant ("Implanted Cohort"), including 20 EFS patients with a Harmony TPV 22 implant, 31 pivotal study patients with a TPV 22 or TPV 25, and 19 pivotal study patients with an earlier design iteration of the TPV 25 (designated as "cTPV 25"[1]) implant. One EFS patient did not receive a Harmony TPV implant after catheterization due to high pulmonary artery pressure. Patient follow-up compliance is detailed in Table 5.

Table 5: Patient Follow-up Compliance

Visit Interval	Number Expected	Number Evaluated
Procedure	71	100% (71)
Discharge	70	100% (70)
1 month	67	100% (67)
6 months	66	100% (66)

Of the 70 patients in the Implanted Cohort, two originally implanted with a cTPV 25 valve were explanted within 24 hours post implant due to valve migration and subsequently received a surgical valve: one on the day of the index procedure and the other the following day. The remaining 68 patients constitutes the "Implanted > 24 Hours Cohort."

C. **Study Population Demographics and Baseline Parameters**

The demographics and baseline characteristics of the study population are typical for a transcatheter pulmonary valve replacement study performed in the U.S., as summarized in Table 6. Of the 71 catheterized patients with medical history data available, 63 included Tetralogy of Fallot as their original diagnosis while the remaining patients had other

[1] The cTPV 25 implant was modified to become the TPV 25 implant due to it not deploying as intended in some cases with challenging anatomies.

diagnoses, the most common of which was pulmonary stenosis. All patients presented with moderate or severe pulmonary regurgitation.

Table 6: Patient Demographics and Baseline Characteristics - Catheterized Cohort

Demographics and Baseline Characteristics	Summary Statistics* (N= 71)
Sex	
Female	40.8% (29/71)
Male	59.2% (42/71)
Age (years)	28.5 ± 12.0 (71)
<22	38.0% (27/71)
12 to < 18	19.7% (14/71)
18 to < 22	18.3% (13/71)
≥22	62.0% (44/71)
Original Diagnosis	
Tetralogy of Fallot	88.7% (63/71)
With pulmonary stenosis	60.6% (43/71)
With pulmonary atresia	7.0% (5/71)
Absent pulmonary valve	0.0% (0/71)
Sub-type not indicated	21.1% (15/71)
Pulmonary stenosis‡	6.0% (3/50)
Pulmonary atresia with intact ventricular septum‡	2.0% (1/50)
Transposition of the Great Arteries	0.0% (0/71)
Truncus arteriosus	0.0% (0/71)
Branch pulmonary artery stenosis§	0.0% (0/21)
Other diagnosis†	8.5% (6/71)
Type of Surgical Patch Material	
None	11.3% (8/71)
Dacron	2.8% (2/71)
Gore-Tex	4.2% (3/71)
Autologous pericardium	11.3% (8/71)
Bovine pericardium	2.8% (2/71)
Unknown/not available	47.9% (34/71)
Other	19.7% (14/71)
Pacemaker or ICD implant	9.9% (7/71)
Pulmonary regurgitation by echocardiography	

Demographics and Baseline Characteristics	Summary Statistics* (N= 71)
None - Mild	0.0% (0/71)
Moderate	4.2% (3/71)
Severe	95.8% (68/71)
Mean RVOT gradient (mmHg) by echocardiogram[l]	9.7 ± 5.3 (56)
Number of previous open heart surgeries	1.3 ± 0.5 (71)
Previous history of endocarditis[‡]	2.0% (1/50)

*Continuous measures - Mean ± SD (Total no.); categorical measures - % (no./Total no.)

†Patients with "other diagnosis" as original diagnosis had: double outlet right ventricle (DORV), atrial septal defect, DORV with pulmonary stenosis, "absent" left pulmonary artery, Noonan syndrome and dysplastic pulmonary valve stenosis, and variant of Tetralogy of Fallot (DORV with pulmonary stenosis, secundum atrial septal defect and patent ductus arteriosus).

‡Information only collected in the 50 patients catheterized in the pivotal study phase.

§Information only collected in the 21 patients catheterized in the EFS phase.

lFifty-six (56) of the 71 patients had available core laboratory echocardiography data.

D. **Safety and Effectiveness Results**

1. Primary Safety Endpoint:

There were no procedure- or device-related deaths reported at 30 days post implant, as summarized in Table 7.

Table 7: Procedure- or Device-Related Mortality at 30 Days Post Implant - Catheterized Cohort

Mortality	Summary Statistics* (N= 71)
Procedure- or device-related	0.0% (0)
Procedure-related	0.0% (0)
Device-related	0.0% (0)

*Event rate (number of patients)

2. Primary Effectiveness Endpoint:

Of the 68 patients in the Implanted > 24 Hours Cohort, three patients had missing echocardiography data due to COVID-19 impact or non-evaluable echocardiography per the imaging core laboratory. A summary of patients with acceptable TPV hemodynamic

function at 6 months without reintervention on the Harmony TPV within the Implanted > 24 Hours Cohort is provided in Table 8, which showed that 58 (89.2%) of the 65 patients with evaluable echocardiography data achieved the primary effectiveness endpoint.

Table 8: Patients with Acceptable TPV Hemodynamic Function at 6 Months without Reintervention on the Harmony TPV – Implanted > 24 Hours Cohort

Primary Effectiveness Endpoint Analysis	Summary Statistics (N=68)
Number of evaluable patients*	65
Number of patients with reintervention	5
Number of patients with mean gradient > 40 mmHg	0
Number of patients with pulmonary regurgitation ≥ moderate	2
Number and percentage of patients with acceptable TPV hemodynamic function without reintervention	58 (89.2%)
Standard error for percentage	3.8%
Two-sided 95% confidence interval†	79.1% - 95.6%

*Three (3) patients implanted with a TPV 25 whose echocardiography data were either missing due to COVID-19 impact or not evaluable per the imaging core laboratory were excluded.

†Two-sided Clopper-Pearson interval

3. Additional Outcome Measures:

Technical Success at Exit from Catheterization Laboratory/Operating Room

The technical success rate at exit from the catheterization laboratory/operating room is summarized in Table 9 for the Implanted Cohort. Technical success was achieved in 92.9% of the patients.

Table 9: Technical Success Rate at Exit from Catheterization Laboratory/ Operating Room - Implanted Cohort

Technical Success	Summary Statistics* (N= 70)
Overall technical success	92.9% (65/70)
No device- or procedural-related mortality	100.0% (70/70)
Successful access, delivery, and retrieval of the delivery system	100.0% (70/70)
Deployment and correct positioning (including minor repositioning if needed) of the single intended device	95.7% (67/70)

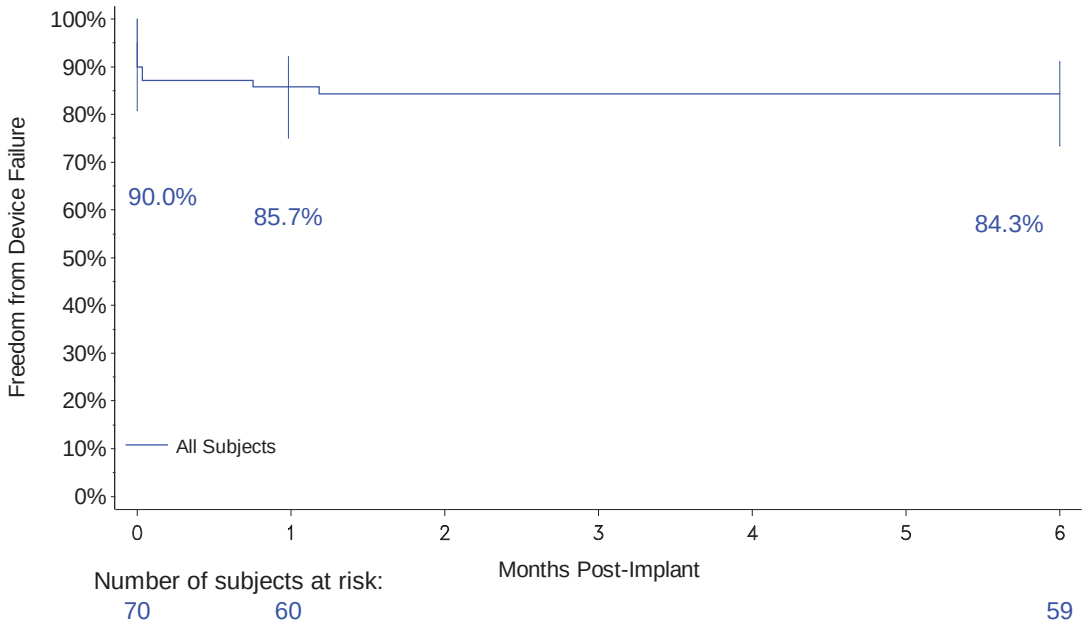
Technical Success	Summary Statistics* (N= 70)
No unplanned or emergency surgery or reintervention related to the device or access procedure	95.7% (67/70)

*Event rate (no./Total no.)

Device Success (or Freedom from Device Failure)

The Kaplan-Meier rate of freedom from device failure through 6 months for the Implanted Cohort is summarized in Figure 3. At 6 months post implant, 84.3% of the patients were free from device failure.

Figure 3: Freedom from Device Failure through 6 Months - Implanted Cohort



Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Eleven (11) patients in the Implanted Cohort met the device failure criteria, as summarized in Table 10.

Table 10: Device Failure - Implanted Cohort

Reasons for Device Failure	Summary Statistics (N= 70)
Device failure*	11/70
Device- or procedural-related mortality	0

Reasons for Device Failure	Summary Statistics (N= 70)
Original intended device not in place	6
Mean RVOT gradient > 40 mmHg	1
Pulmonary regurgitation ≥ moderate	4
Surgical reoperation or catheter reintervention	7
Structural performance (migration, embolization, detachment, major stent fracture, hemolysis, thrombosis, endocarditis)	6
Erosion or RVOT/PA rupture	1
Paravalvular leak ≥ moderate	4

*Eleven patients included 3 patients from the EFS phase and 8 from the pivotal study phase. The reasons listed for device failure are not mutually exclusive (a given patient could have more than one device failure reasons).

Procedural Success

Procedural success was evaluated for the pivotal phase only because not all components per definition of the endpoint were captured in the feasibility phase of the study. The pivotal phase included 50 patients in the Implanted Cohort. The rate of procedural success at 30 days is summarized in Table 11 for the Implanted Cohort of the pivotal phase, which showed an overall procedural success rate of 84.0%.

Table 11: Procedural Success at 30 Days - Implanted Cohort (Pivotal Phase)

Procedural Success	Summary Statistics* (N= 50)
Overall procedure success	84.0% (42/50)
No device failure	84.0% (42/50)
No life-threatening major bleed†	100.0% (48/48)
No major vascular or cardiac structural complications required unplanned reintervention or surgery†	97.9% (47/48)
No stage 2 or 3 acute kidney injury (including new dialysis)†	100.0% (48/48)
No pulmonary embolism†	100.0% (48/48)

Procedural Success	Summary Statistics* (N= 50)
No severe heart failure or hypotension requiring intravenous inotrope, ultrafiltration, or mechanical circulatory support†	100.0% (48/48)
Prolonged intubation ≤ 48 hours	100.0% (50/50)

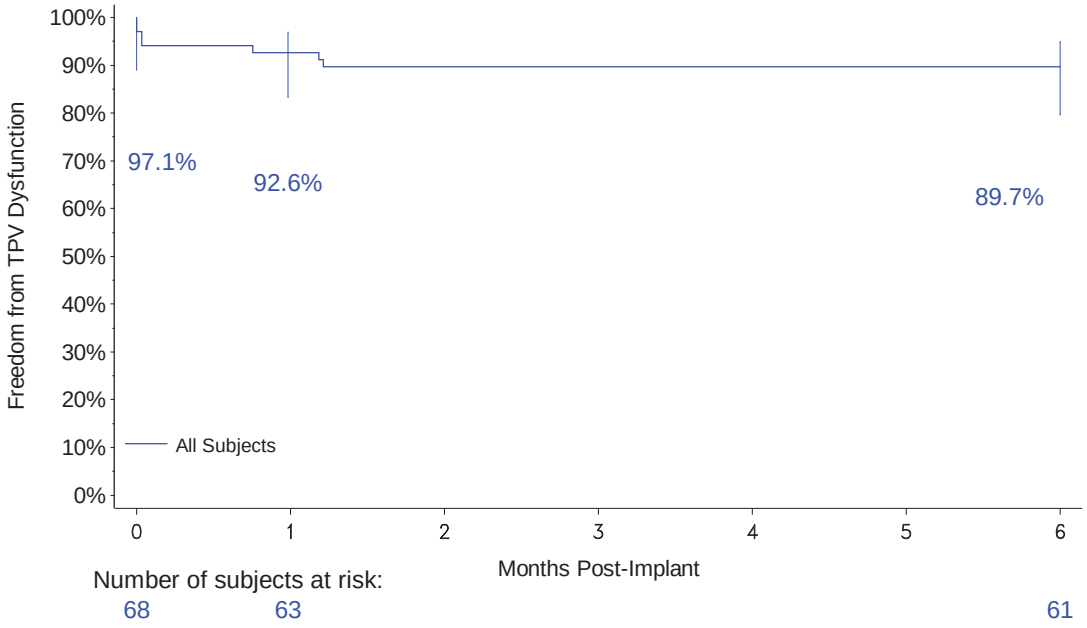
*Event rate (no./Total no.).

†Information not available for 2 of the 50 patients.

Freedom from TPV Dysfunction

The Kaplan-Meier rate of freedom from TPV dysfunction through 6 months for the Implanted > 24 Hours Cohort is shown in Figure 4. At 6 months post implant, 89.7% of the patients were free from TPV dysfunction.

Figure 4: Freedom from TPV Dysfunction through 6 Months – Implanted >24 Hours Cohort



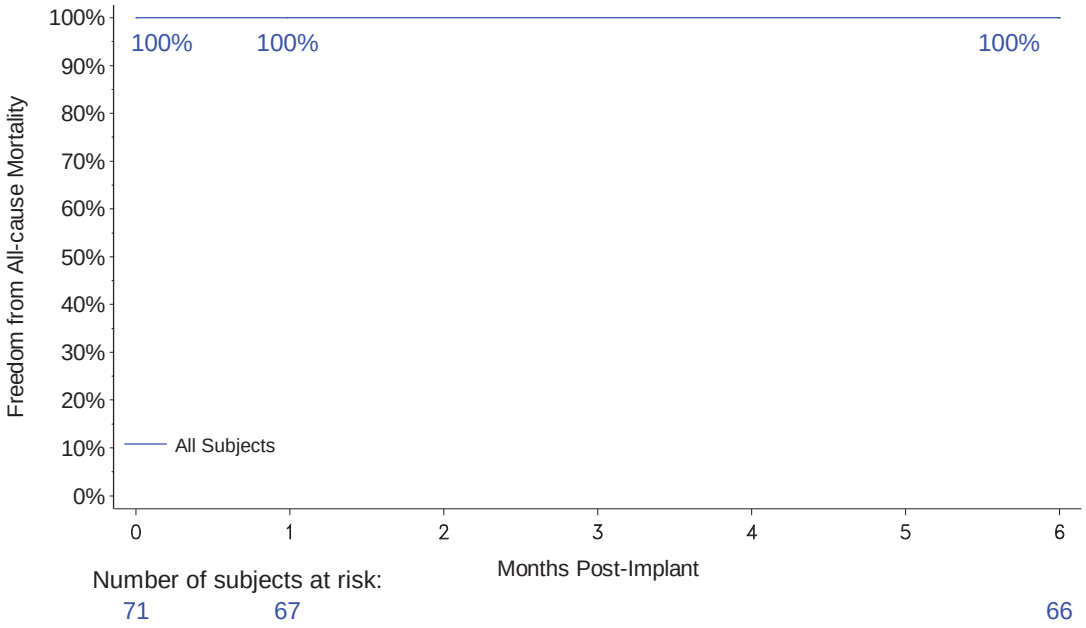
Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

All-cause Mortality

The Kaplan-Meier rate of freedom from all-cause mortality through 6 months for the Catheterized Cohort is shown in Figure 5. There was no death reported in the catheterized

patients at 6 months.

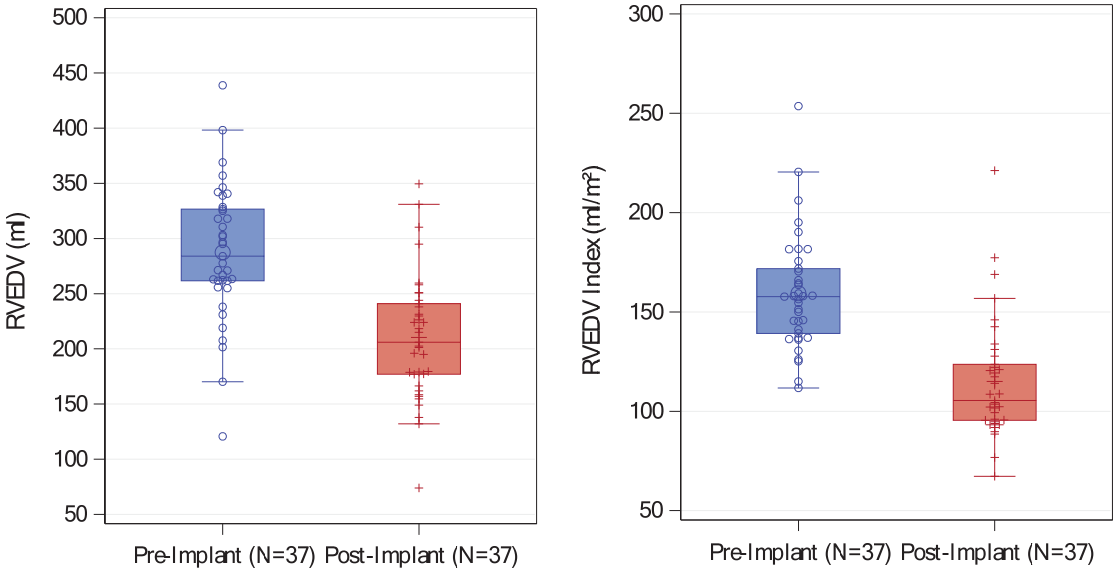
Figure 5: Freedom from All-Cause Mortality – Catheterized Cohort



Characterization of Right Ventricle Remodeling

Right ventricular remodeling post Harmony TPV implant was characterized via cardiovascular magnetic resonance (CMR) imaging, where not contraindicated. There were a significant number of patients with CMR contraindication, such as pacemaker implantation. The paired right ventricular end diastolic volume (RVEDV) and RVEDV index, pulmonary regurgitation fraction (PRF), and net right ventricular stroke volume pre- and post-implant are shown in Figures 6 through Figure 8, respectively. The post-implant timepoint was 6 months for patients implanted in the pivotal stage and 12 months for patients implanted in the feasibility stage (CMR was not performed at 6 months in the feasibility stage). The RVEDV decreased from 287.5 ± 61.9 to 210.3 ± 56.7 ml, with the corresponding RVEDV index decreasing from 159.4 ± 28.9 to 115.0 ± 29.9 ml/m^2; the net right ventricular stroke volume increased from 79.5 ± 26.2 to 91.0 ± 24.2 ml/beat); and the pulmonary regurgitant fraction decreased from 40.5 ± 11.6% to 2.4 ± 3.3%.

Figure 6: Right Ventricular End Diastolic Volume (RVEDV) and RVEDV Index Pre- and Post-Implant – Implanted Cohort



(a) RVEDV (b) RVEDV Index

Figure 7: Pulmonary Regurgitation Fraction (PRF) Pre- and Post-Implant – Implanted Cohort

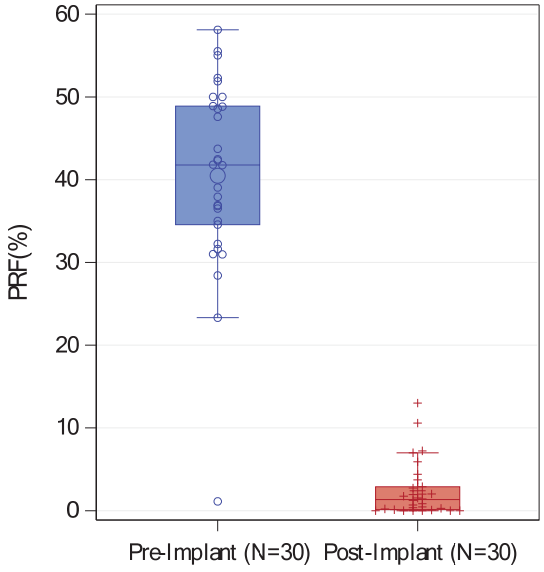
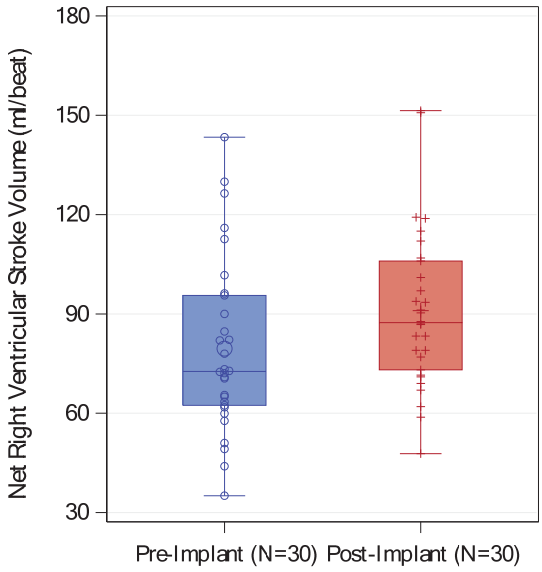


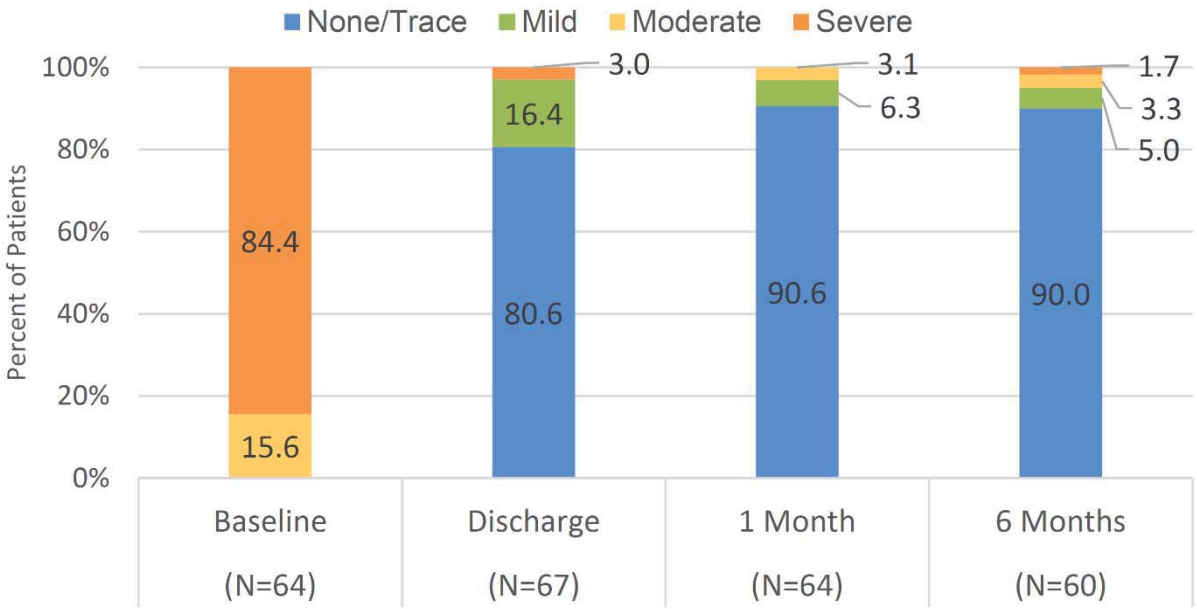
Figure 8: Net Right Ventricular Stroke Volume Pre- and Post-Implant – Implanted Cohort



Pulmonary Regurgitation

Pulmonary regurgitation through 6 months assessed by echocardiography is shown in Figure 9. The proportion of patients with severe pulmonary regurgitation was 1.7% at 6 months compared to 84.4% at baseline.

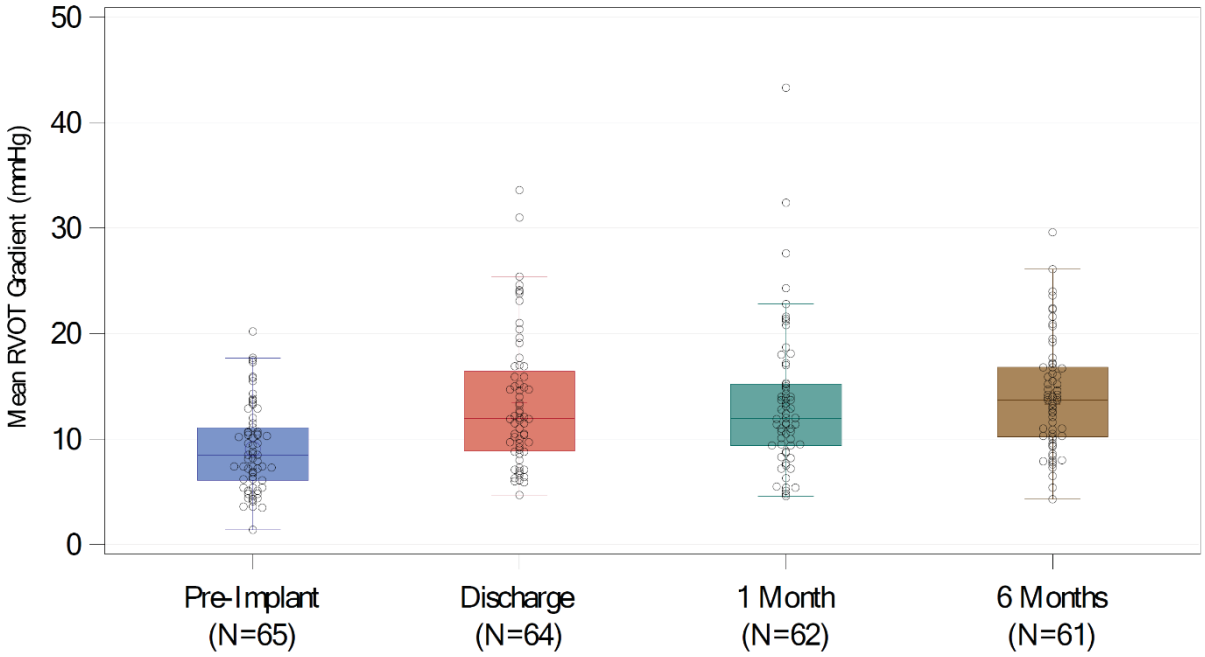
Figure 9: Pulmonary Regurgitation by Visit – Implanted Cohort



RVOT Gradient

The RVOT gradient over time post implant is shown in Figure 10. At discharge the mean RVOT gradient was 13.5 ± 6.3 mmHg and remained stable through 6 months (14.0 ± 5.3 mmHg).

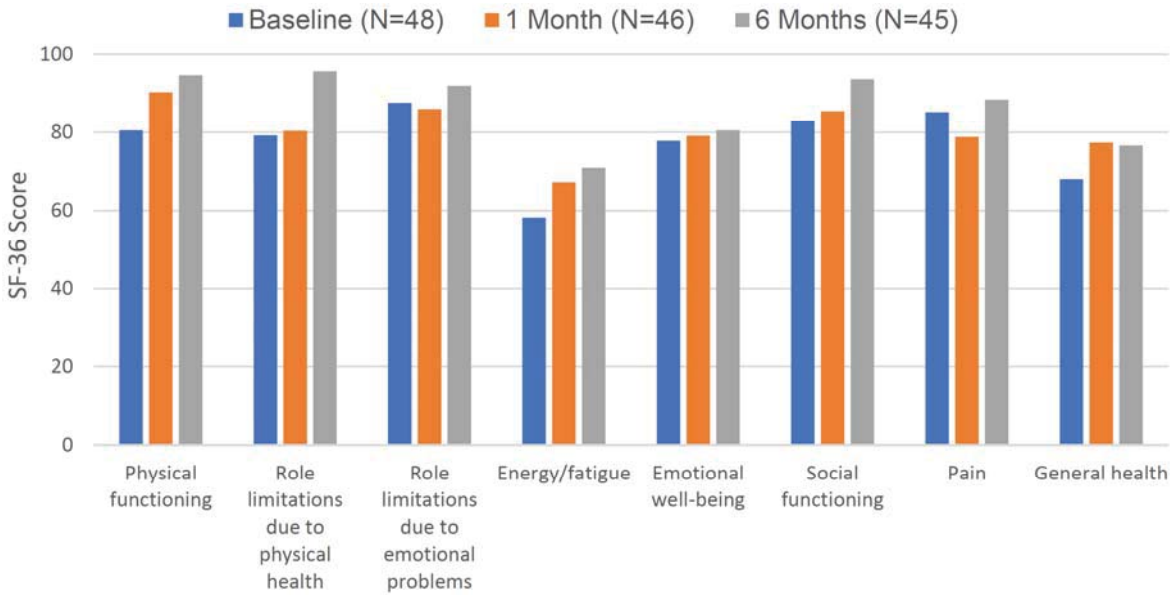
Figure 10: Mean RVOT Gradient by Visit – Implanted Cohort



Quality of Life

Quality of life over time was assessed in the Implanted > 24 Hours Cohort using the 36-Item Short Form Survey (SF-36). The SF-36 scores through 6 months for patients implanted in the pivotal stage are shown in Figure 11. Gains were observed across the mean scores of all eight scales at 6 months post-implant, with the most gain in the areas of physical functioning (80.5 ± 25.6 at baseline vs. 94.6 ± 8.8 at 6 months) and role limitations due to physical health (79.2 ± 33.9 at baseline vs. 95.6 ± 18.7 at 6 months). The assessment was not performed in patients implanted in the feasibility stage.

Figure 11: SF-36 Score by Visit – Implanted > 24 Hours Cohort (Pivotal Phase)



Adverse Events

The CEC-adjudicated adverse events at 6 months are summarized in Table 12 for the for Catheterized Cohort, stratified by the study phase and implant model.

Table 12: CEC-Adjudicated Adverse Events at 6 Months – Catheterized Cohort

Adverse Events	Summary Statistics*			
	All Subjects (N=71)	Feasibility Phase	Pivotal Phase	
		TPV 22 (N=21)	TPV 22 & TPV 25 (N=31)	cTPV 25 (N=19)
All-cause mortality	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Embolization of the TPV	2.8% (2)	0.0% (0)	0.0% (0)	10.5% (2)
Migration of the TPV	4.2% (3)	9.5% (2)	3.2% (1)	0.0% (0)
Misorientation of the TPV	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Misplacement of the TPV	1.4% (1)	0.0% (0)	0.0% (0)	5.3% (1)
Other device related AE†	7.0% (5)	4.8% (1)	0.0% (0)	21.1% (4)
Collapse of valve frame	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Endocarditis	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Erosion	1.4% (1)	4.8% (1)	0.0% (0)	0.0% (0)

Adverse Events	Summary Statistics*			
	All Subjects (N=71)	Feasibility Phase	Pivotal Phase	
		TPV 22 (N=21)	TPV 22 & TPV 25 (N=31)	cTPV 25 (N=19)
Stent fracture: major	1.4% (1)	4.8% (1)	0.0% (0)	0.0% (0)
Thrombosis of the TPV	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Structural deterioration	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Valve dysfunction	4.2% (3)	14.3% (3)	0.0% (0)	0.0% (0)
Stenosis	4.2% (3)	14.3% (3)	0.0% (0)	0.0% (0)
Regurgitation	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Stenosis & regurgitation	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Paravalvular leak	8.5% (6)‡	4.8% (1)‡	3.2% (1)	21.1% (4)
Major	1.4% (1)	4.8% (1)	0.0% (0)	0.0% (0)
Minor	7.0% (5)	0.0% (0)	3.2% (1)	21.1% (4)
Coronary compression causing myocardial ischemia	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Perforation of the heart	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Perforation of the vessel	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
RVOT rupture or dissection	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Congestive heart failure	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Cardiac arrest	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Myocardial infarction	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Hemorrhage	7.0% (5)	0.0% (0)	9.7% (3)	10.5% (2)
Major or life threatening	0/0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Minor	7.0% (5)	0.0% (0)	9.7% (3)	10.5% (2)
Pulmonary thromboembolism	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Pseudoaneurysm	1.4% (1)	0.0% (0)	3.2% (1)	0.0% (0)
Brachial plexus injury	1.4% (1)	0.0% (0)	3.2% (1)	0.0% (0)
Arrhythmia	23.9% (17)	4.8% (1)	25.8% (8)	42.1% (8)
Heart block, 3rd degree	1.4% (1)	0.0% (0)	0.0% (0)	5.3% (1)
Supraventricular tachycardia	2.8% (2)	0.0% (0)	6.5% (2)	0.0% (0)
Ventricular premature beats	5.6% (4)	0.0% (0)	6.5% (2)	10.5% (2)

Adverse Events	Summary Statistics*			
	All Subjects (N=71)	Feasibility Phase	Pivotal Phase	
		TPV 22 (N=21)	TPV 22 & TPV 25 (N=31)	cTPV 25 (N=19)
Ventricular tachycardia	14.1% (10)	4.8% (1)	12.9% (4)	26.3% (5)

*Event rate (number of patients)

†Other device-related adverse events included four TPV maldeployments with the cTPV25 implant and one frame collapse.

‡One patient had a minor paravalvular leak reported followed by a major paravalvular leak reported, which resulted in the Harmony valve being explanted. This is reported as one major paravalvular leak event.

Surgical Reintervention

The results of surgical reinterventions at 6 months post implant are summarized in Table 13, stratified by the study phase and implant model. Four patients had their Harmony TPV explanted and a surgical valve placed by 6 months.

Table 13: Surgical Reinterventions at 6 Months – Implanted Cohort

Surgical Reintervention	Summary Statistics*			
	All Patients (N= 70)	Feasibility Phase	Pivotal Phase	
		TPV 22 (N=20)	TPV 22 & TPV 25 (N=31)	cTPV 25 (N=19)
Explant of the TPV	5.7% (4)	10.0% (2)	0.0% (0)	10.0% (2)
Repair or alteration of RVOT, TPV conserved	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)

*Event rate (number of patients)

Catheter Reintervention

The results of catheter reinterventions at 6 months post implant are summarized in Table 14, stratified by the study phase and implant model. Three patients had 6 total catheter reinterventions performed through 6-month follow-up, with some patients having more than one type of catheter reintervention.

Table 14: Catheter Reinterventions at 6 Months – Implanted Cohort

Catheter Reintervention	Summary Statistics*			
	All Patients (N= 70)	Feasibility Phase	Pivotal Phase	
		TPV 22 (N=20)	TPV 22 & TPV 25 (N=31)	cTPV 25 (N=20)
Implantation of another TPV	2.9% (2)	0.0% (0)	0.0% (0)	10.5% (2)
Stent placement, Branch PA	2.9% (2)	0.0% (0)	0.0% (0)	10.5% (2)
Stent placement, other	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Balloon angioplasty of the TPV	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Other†	2.9% (2)	0.0% (0)	0.0% (0)	10.5% (2)

*Event rate (number of patients)
†Reinterventions classified by sites as "other" included balloon angioplasty and balloon inflation.

4. Subgroup Analyses

The protocol specified subgroup analyses of the primary effectiveness endpoint by age and by gender.

Acceptable Hemodynamic Performance Stratified by Age

The number of patients in the Implanted >24 Hours Cohort with acceptable TPV hemodynamic function at 6 months without reintervention post implant stratified by age ("< 22 years" vs. "≥ 22 years") is shown in Table 15. The results are comparable between the "< 22 years" subgroup and the "≥ 22 years" subgroup.

Table 15: Patients with Acceptable TPV Hemodynamic Function at 6 Months Stratified by Age – Implanted > 24 Hours Cohort

Patients with Acceptable TPV Hemodynamic Function at 6 Months	Summary Statistics (N=68)	
	< 22 years (N=27)	≥ 22 years (N=41)
Number of evaluable patients	27	38
Number and percentage of patients with acceptable TPV hemodynamic function without reintervention	24 (88.9%)	34 (89.5%)
Standard error for percentage	6.0%	5.0%
Two-sided 95% confidence interval*	70.8% - 97.6%	75.2% - 97.1%

*Two-sided Clopper-Pearson interval

Acceptable Hemodynamic Performance Stratified by Gender

The number of patients in the Implanted >24 Hours Cohort with acceptable TPV hemodynamic function at 6 months without reintervention post implant stratified by gender is shown in Table 16. The results are comparable between the female and male subgroups.

Table 16: Patients with Acceptable TPV Hemodynamic Function at 6 Months Stratified by Gender – Implanted > 24 Hours Cohort

Patients with Acceptable TPV Hemodynamic Function at 6 Months	Summary Statistics (N=68)	
	Female (N=28)	Male (N=40)
Number of evaluable patients	26	39
Number and percentage of patients with acceptable TPV hemodynamic function without reintervention	23 (88.5%)	35 (89.7%)
Standard error for percentage	6.3%	4.9%
Two-sided 95% confidence interval*	69.8% - 97.6%	75.8% - 97.1%

*Two-sided Clopper-Pearson interval.

5. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population. Rather, pediatric data were included in the application to support the pediatric indication and no extrapolation was necessary.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The Harmony TPV clinical study included 107 investigators, of which none were full-time or part-time employees of the sponsor and two had disclosable financial interests/ arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None
- Significant payment of other sorts: 4
- Proprietary interest in the product tested held by the investigator: None
- Significant equity interest held by investigator in sponsor of covered study: None

The applicant has adequately disclosed the financial interest/arrangements with clinical

investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the clinical study, 89.2% of the patients had acceptable hemodynamic function at 6 months without reintervention on the Harmony TPV. Of the implanted patients followed out to 6 months, 84.4% of the patients had severe pulmonary regurgitation at pre-implant. The proportion of patients with severe pulmonary regurgitation decreased from 84.4% at baseline to 1.7% at 6 months. The mean RVOT gradient remained stable from discharge (13.5 ± 6.3 mmHg) to 6 months (14.0 ± 5.3 mmHg). Positive changes in right ventricular function were seen post implant, as evidenced by the reduction in right ventricular end diastolic volume (RVEDV: 287.5 ± 61.9 to 210.3 ± 56.7 ml; RVEDV index: 159.4 ± 28.9 to 115.0 ± 29.9 ml/m^2), increase in net right ventricular stroke volume (79.5 ± 26.2 to 91.0 ± 24.2 ml/beat), and decrease in pulmonary regurgitant fraction (40.5 ± 11.6% to 2.4 ± 3.3%).

The procedure success rate was 84% at 30 days in the pivotal phase of the clinical study. For patients implanted with a Harmony TPV for more than 24 hours, 89.7% of the patients were free from TPV dysfunction at 6 months. The overall freedom from device failure rate at 6 months was 84.3%.

Post implant, patients experienced the most gain in quality of life, as assessed by the SF-36 survey, in the areas of physical functioning (94.6 ± 8.8 at 6 months vs. 80.5 ± 25.6 at baseline) and role limitations due to physical health (95.6 ± 18.7 at 6 months vs. 79.2 ± 33.9 at baseline).

B. Safety Conclusions

The risks of the device are based on non-clinical laboratory and animal studies, as well as data collected in a clinical study conducted to support PMA approval as described above. The results from the non-clinical laboratory and animal studies performed on the Harmony TPV system demonstrate that the device meets all specifications and is suitable for long-term implant.

All catheterized patients were free from procedure- or device-related mortality at 30 days or all-cause mortality at 6 months. Technical success at exit from catheterization

laboratory/operating room was achieved in 92.9% of all implanted patients. Surgical and transcatheter reinterventions occurred in 5.7% and 2.9% of the implanted patients, respectively, at 6 months. The adverse events through 6 months included arrhythmia (23.9%; 14.1% ventricular tachycardia), paravalvular leak (8.5% with 1.4% major), minor hemorrhage (7.0%), pulmonary stenosis (4.2%), and migration (4.2%) and embolization (2.8%) of the TPV.

C. Benefit-Risk Determination

The probable benefits of the Harmony TPV include improved pulmonary valve hemodynamic performance and improved quality of life at 6 months.

The probable risks of the Harmony TPV include device- and procedure-related complications such as embolization and migration of the implant, arrhythmia, paravalvular leak, and bleeding.

1. Patient Perspectives

   This application did not include specific information on patient perspectives for this device. However, since transcatheter pulmonary valve replacement provides a less invasive alternative to surgical pulmonary valve replacement, FDA believes that many patients would prefer the transcatheter pulmonary valve replacement therapy. However, the long-term durability of the transcatheter pulmonary valve replacement therapy compared to surgical pulmonary valve replacement therapy has not been established. Patients should discuss available treatment options with their heart care team to select the appropriate therapy.

In conclusion, given the available information above, the data support that for patients with severe pulmonary regurgitation who have a native or surgically-repaired RVOT, the probable benefits of the Harmony TPV outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the Harmony TPV System for the management of pediatric and adult patients with severe pulmonary regurgitation who have a native or surgically-repaired right ventricular outflow tract and are clinically indicated for surgical pulmonary valve replacement.

XIII. CDRH DECISION

CDRH issued an approval order on March 26, 2021. The final conditions of approval cited in the approval order are described below:

The applicant must conduct the following two post-approval studies:

1. **Continued Follow-up of the Harmony TPV IDE Cohort**: This study will be conducted

in accordance with the protocol, entitled, "Clinical Investigation Plan Addendum – Post Approval (PAS) Phase" (Version 1.0), dated March 22, 2021. The study will consist of 82 patients enrolled in the IDE study (including the Continued Access Protocol investigation). The objective of the study is to characterize the clinical outcomes annually, unless otherwise specified, through 10 years post implant. The safety and effectiveness endpoints include device success, freedom from TPV dysfunction, freedom from all-cause mortality, serious device-related adverse events, characterization of right ventricular remodeling (6 months, 2 years, 5 years and 10 years), quality of life score (SF-36), and reoperation.

2. **Harmony TPV New Enrollment Study:** This study will be conducted in accordance with the protocol, entitled, "Harmony Post-Approval Study Clinical Investigation Plan" (Version 1.0), dated March 22, 2021. The study will enroll 150 patients at up to 30 sites that did not participate in the Harmony TPV IDE Study. The objective of the study is to characterize the real-world performance of the Harmony TPV through 10 years post implant. The safety and effectiveness endpoints include proportion of patients without valve intervention and with acceptable hemodynamic function at 6 months, procedure success at 30 days, as well as freedom from all-cause mortality, freedom from reoperation, freedom from catheter reintervention, freedom from TPV dysfunction, and serious procedure- and device-related adverse events at 6 months and annually through 10 years.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See final approved labeling (Instructions for Use).

Hazards to health from use of the device: See indications, contraindications, warnings, precautions, and adverse events in the final labeling (Instructions for Use).

Post-approval requirements and restrictions: See approval order.