SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Pulmonary Valve Prosthesis, Percutaneously Delivered
Device Trade Name:	Melody™ Transcatheter Pulmonary Valve, models PB1016 and PB1018 Ensemble™ Transcatheter Valve Delivery System, models NU1018, NU1020, and NU1022
Device Procode:	NPV
Applicant Name and Address:	Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN 55112
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P140017
Date of FDA Notice of Approval:	January 27, 2015

Priority Review: Granted priority review status on August 21, 2014 because the device represents a breakthrough technology.

The Melody Transcatheter Pulmonary Valve (TPV) and the Ensemble Transcatheter Valve Delivery System (DS) were originally approved under Humanitarian Device Exemption (HDE), H080002, on January 25, 2010. The Summary of Safety and Probable Benefit (SSPB) to support the HDE approval is available on the CDRH website (http://www.accessdata.fda.gov/cdrh_docs/pdf8/H080002b.pdf) and is incorporated by reference here. The current PMA application is a conversion from the original HDE.

II. INDICATIONS FOR USE

The Melody TPV is indicated for use as an adjunct to surgery in the management of pediatric and adult patients with the following clinical conditions:

- Existence of a full (circumferential) right ventricular outflow tract (RVOT) conduit that was equal to or greater than 16 mm in diameter when originally implanted, and
- Dysfunctional RVOT conduit with a clinical indication for intervention, and:
    - regurgitation: ≥ moderate regurgitation, and/or
    - stenosis: mean RVOT gradient ≥ 35 mmHg

III. CONTRAINDICATIONS

There are no known contraindications for the Melody TPV.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the labeling (Instructions for Use) for the Melody TPV system.

V. DEVICE DESCRIPTION

The Melody TPV system consists of 2 components: the Melody TPV and the Ensemble DS.

TPV

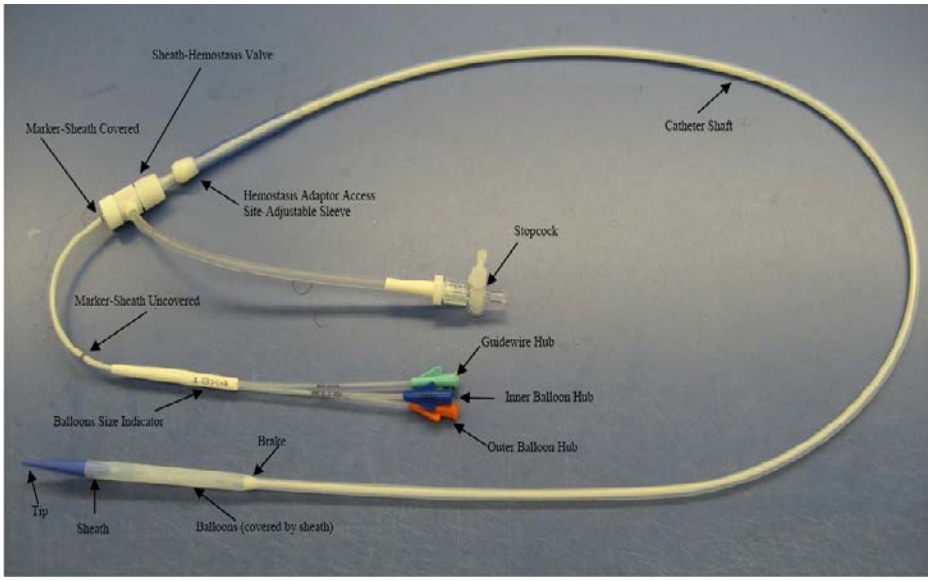
The Melody TPV consists of a bovine jugular vein (BJV) with a native valve, sutured into a platinum iridium frame (Figure 1). It is available in 2 sizes: a 16 mm BJV which can be expanded to 20 mm and an 18 mm BJV which can be expanded to 22 mm. Both the 16 mm and 18 mm sizes of Melody TPV utilize the same platinum iridium frame, which is expanded at implantation to the respective size.

Figure 1: Melody Transcatheter Pulmonary Valve

Ensemble DS

The Ensemble DS is designed to deliver a mounted Melody TPV via venous access to a failing RVOT conduit previously implanted for the repair of congenital pathologies (Figure 2). It consists of a balloon-in-balloon catheter with a retractable sheath, and has a 22 Fr crossing profile. Both balloons are made of nylon. The delivery system comes in outer balloon sizes of 18, 20, and 22 mm (NU1018, NU1020, and NU1022, respectively). It is compatible with a 0.035-inch guidewire.

Figure 2: Ensemble Delivery System



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are two alternatives for the correction of dysfunctional RVOT conduits: balloon angioplasty and surgical replacement of the RVOT conduit with either a homograft or conduit with an integral bioprosthetic 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 Melody TPV system is commercially available in the following country or geography and has not been withdrawn from marketing for any reason related to its safety or effectiveness:

- Latin America
- Asia Pacific
- Central and Eastern Europe, Central Asia
- United States of America
- Australia/New Zealand
- United States of America
- Saudi Arabia
- Europe
- Canada

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential procedural complications that may result from the implantation of the Melody TPV include:

- Rupture of the RVOT conduit
- Compression of a coronary artery
- Perforation of a major blood vessel
- Embolization or migration of the TPV
- Perforation of a heart chamber
- Arrhythmias
- Allergic reaction to contrast media
- Cerebrovascular events (transient ischemic attack (TIA), cerebrovascular accident (CVA))
- Infection/sepsis
- Fever
- Hematoma
- Radiation-induced erythema, blistering, or peeling of the skin
- Pain, swelling, or bruising at the catheterization site

Potential device-related adverse events that may occur following TPV implantation include:

- Stent fracture[1]
- Stent fracture resulting in recurrent obstruction
- Endocarditis
- Embolization or migration of the TPV
- Valvular dysfunction (stenosis or regurgitation)
- Paravalvular leak
- Valvular thrombosis
- Pulmonary thromboembolism
- Hemolysis

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

IX. SUMMARY OF PRECLINICAL STUDIES

A summary of previously reported preclinical studies can be found in the Summary of Safety and Probable Benefit (SSPB) for the original HDE (http://www.accessdata.fda.gov/cdrh_docs/pdf8/H080002b.pdf).

X. SUMMARY OF CLINICAL STUDIES

Medtronic has been conducting two prospective clinical studies in the United States that support a reasonable assurance of safety and effectiveness in subjects treated with the Melody TPV:

- Melody TPV Long-term Follow-up Post Approval Study (PAS)

[1] The term "stent fracture" refers to the fracture of the Melody™ TPV. However, in subjects with multiple stents in the RVOT it is difficult to definitively attribute stent fractures to the Melody™ frame versus another stent.

- Melody TPV New Enrollment PAS

The PMA application includes the interim results and a retrospective pooling analysis of these two PAS'. Additionally, it includes a supplemental dataset from the Melody TPV European and Canadian Post-Market Surveillance Study (PMSS).

X.1. Melody TPV Long-term Follow-up PAS

A. Study Design

The Melody TPV Long-term Follow-up PAS is a prospective, non-randomized, multi-center study conducted at 5 centers in the United States. The study consists of subjects who received the implant during the pre-market IDE trial. The purpose of the study is to characterize the longer-term performance of the Melody TPV in dysfunctional RVOT conduits.

An independent Data Safety Monitoring Board (DSMB), Clinical Events Committee (CEC), and imaging core laboratory were utilized in the IDE trial through HDE approval in 2010. All subjects had imaging data through 1 year analyzed by the imaging core laboratory. The Long-term Follow-up PAS study continues to use an independent pathology core laboratory to analyze explanted devices and Cardiopulmonary Exercise Testing (CPET) core laboratory for review and interpretation of CPET exams.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the pre-market IDE study was limited to patients who met the following inclusion criteria:

   - Age ≥ 5 years of old
   - Weight ≥ 30 kg
   - Existence of a full (circumferential) RVOT conduit ≥ 16 mm in diameter when originally implanted, or a stented bioprosthesis with a rigid circumferential sewing ring in the RVOT that has an internal diameter ≥ 18 mm and ≤ 22 mm when originally implanted
   - Any of the following by transthoracic echocardiography
     - For patients in NYHA Classification II, III, or IV:
       - Moderate (3+) or severe (4+) pulmonary regurgitation, or
       - Mean RVOT gradient ≥ 35 mmHg
     - For patients in NYHA Classification I:
       - Severe (4+) pulmonary regurgitation with RV dilatation (Z-score for tricuspid annular diameter ≥2.0) or dysfunction (RV fractional area change < 40%), or
       - Mean RVOT gradient ≥ 40 mmHg

   Patients were not permitted to enroll in the pre-market IDE study if they met any of the following exclusion criteria:

- Active endocarditis
- 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
- Patient or guardian unwilling or unable to provide written informed consent or comply with follow-up requirements
- Obstruction of the central veins (including the superior and inferior vena cava, bilateral iliac veins) such that the delivery system cannot be advanced to the heart via transvenous approach from either femoral vein or internal jugular vein
- Positive urine or serum pregnancy test 24 hours prior to procedure in female patients of child bearing potential
- Known intravenous drug abuse

2. Follow-up Schedule

The study will have annual clinic visits through 5 years, with clinical assessment, echocardiography, chest X-ray, and cardiopulmonary exercise testing (CPET) at each visit. The applicant has voluntarily extended the follow-up to 10 years, with clinical assessment, echocardiography, and chest X-ray at the year 6-10 visits. Participation in the year 6-10 follow-up is voluntary for the subjects.

3. Clinical outcomes

The primary outcome measure is TPV dysfunction at 5 years after TPV implant, which is a composite measure defined as follows:

- RVOT reoperation for conduit dysfunction or device-related reasons, or
- Catheter re-intervention on the TPV, or
- Hemodynamic dysfunction of the TPV (moderate or greater PR and/or a mean RVOT gradient > 40 mmHg)

Pre-specified secondary outcome measures include:

(1) Freedom from TPV dysfunction at 10 years
(2) Procedural success composite defined as follows:
    - TPV fixated within the desired location
    - Right ventricle (RV)-pulmonary artery (PA) peak-to-peak gradient < 35 mmHg post-implantation
    - Less than mild pulmonary regurgitation (PR) by angiography post-implantation
    - Free of explant at 24 hours post-implantation
(3) Serious procedural adverse events;
(4) Serious device-related adverse events
(5) Stent fracture (major and minor)
(6) Catheter re-intervention on the TPV
(7) Surgical replacement of the RVOT conduit
(8) Death (all-cause, procedural, and device-related)

(9) Functional status (New York Heart Association (NYHA) classification)
(10) Hemodynamic performance

The above outcome measures were identified to demonstrate safety and effectiveness of the Melody TPV, as they address the most important clinical aspects of the device's ability to restore pulmonary valve competence, to extend the life of a dysfunctional RVOT conduit, and to delay the need for surgical conduit replacement while maintaining safety for the patient.

4. Accountability of Study Subjects

A total of 171 subjects were enrolled in the original IDE study between January 31, 2007 and January 12, 2010. In total, 167 subjects underwent catheterization for potential implantation of the Melody TPV, with 150 subjects subsequently receiving the valve.

B. Study Population Demographics and Baseline Parameters

Table 1 presents the subject demographics and baseline characteristics analyzed for the enrolled subjects. The study population consisted of 107 male and 64 female subjects with a mean age of 21.8 ± 9.8 (range 7 to 53 years). Tetralogy of Fallot was the most common original diagnosis (50.3%), followed by aortic valve disease in subjects having undergone a Ross procedure (20.5%).

Table 1: Long-term Follow-up PAS: Subject Demographics – Enrolled Cohort (N=171)

Assessment	Enrolled Cohort (N=171)
Gender	
Male	62.6% (107/171)
Female	37.4% (64/171)
Age (years)	
n	171
Mean ± SD	21.8±9.8
Median [Min, Max]	19.0 [7.0, 53.0]
Original diagnosis	
Tetralogy of Fallot	50.3% (86/171)
Aortic valve disease (Ross)	20.5% (35/171)
Isolated pulmonary stenosis	1.8% (3/171)
Truncus arteriosus	10.5% (18/171)
Transposition of the great arteries	10.5% (18/171)
Double outlet right ventricle	4.7% (8/171)
Other[1]	1.8% (3/171)
RVOT conduit type	
Homograft	71.9% (123/171)
Biological valved conduit	14.6% (25/171)
Bioprosthesis	4.7% (8/171)
Synthetic	4.7% (8/171)
Other	4.1% (7/171)
RVOT conduit size (mm) when originally implanted	

Assessment	Enrolled Cohort (N=171)
n	163
Mean ± SD	21.0±2.6
Median [Min, Max]	21.0 [11.0, 28.0]
Bioprosthesis size (mm) when originally implanted	
n	8
Mean ± SD	21.6±2.3
Median [Min, Max]	22.0 [18.0, 25.0]

[1] Other original diagnosis included: pulmonary atresia with intact ventricular septum (n=1); double outlet right ventricle (DORV) with malposed great arteries, ventricular septal defect (VSD), and coarctation of the aorta (n=1); pulmonary stenosis with atrial septal defect (ASD) (n=1).

C. Safety and Effectiveness Results

Data presented herein are interim results through March 1, 2014. The mean length of follow-up was 52.9 ± 15.6 months. As follow-up is ongoing, primary outcomes have not been reached and thus are not yet reported.

1. Procedural Data

A summary of procedural data of those enrolled patients who underwent cardiac catheterization for the purpose of TPV implantation is provided in Table 2. All procedures were performed under general anesthesia. The percutaneous femoral venous approach was used in the majority of subjects (94.6%); however, in some patients, internal jugular vein (4.8%) or subclavian vein (0.6%) access was used.

Table 2: Long-term Follow-up PAS: Procedural Data – Catheterized Cohort (N=167)

Assessment	Catheterized Cohort (N=167)
Anesthesia	
General	100.0% (167/167)
Local	0.0% (0/167)
Venous site access	
Femoral vein	94.6% (158/167)
Jugular vein	4.8% (8/167)
Subclavian vein	0.6% (1/167)
Concomitant procedures[1]	
No concomitant procedures	59.3% (99/167)
Stent placement, peripheral PA	4.2% (7/167)
Balloon angioplasty, peripheral PA	4.8% (8/167)
Stent placement, RVOT Conduit	32.3% (54/167)
Placement of intravascular coil	0.6% (1/167)
Closure of ASD or PFO	0.6% (1/167)
Closure of VSD	0.0% (0/167)
Other[2]	4.8% (8/167)
Total fluoroscopy time (minutes)	
n	165
Mean ± SD	43.6±21.7
Median [Min, Max]	40.0 [9.0, 131.0]
Total procedure time (minutes)	
n	165
Mean ± SD	174.1±65.4

Assessment	Catheterized Cohort (N=167)
Median [Min, Max]	167.0 [34.0, 448.0]
Length of hospital stay (days)	
n	165
Mean ± SD	1.2±0.9
Median [Min, Max]	1.0 [0.0, 7.0]

[1] Subjects may have had more than one concomitant procedure
[2] Other concomitant procedures included: electrophysiology study (n=3), stenting of the inferior vena cava (n=1), aneurysm closure (n=1), transesophageal echocardiography (n=1), coronary artery stenting (n=1), balloon angioplasty and interposition conduit-RPA graft (n=1).

Concomitant procedures were not allowed per the clinical investigation plan (CIP) in the first 35 subjects (implanted cohort). During the course of the IDE study, the CIP was amended to allow for concomitant vascular interventional procedures during the Melody TPV procedure, as the standard of care for the management of the Melody TPV target population was evolving. Pre-stenting of the RVOT landing site for the Melody TPV was one concomitant procedure performed during the IDE study. The protocol did not require use of a particular type or number of stents for the pre-stenting procedure. The protocol also did not specify any criteria for performing the pre-stenting procedure. All decisions to pre-stent were made by the investigating physicians. Thus, study subjects were implanted with a variety (in number and type) of stents and the Melody TPV. In all, 54 of 115 (47.0%) implanted patients eligible for pre-stenting received concomitant pre-stenting of the RVOT conduit.

2. Safety Results

Acute Procedure-related Serious Adverse Events

Of the 167 subjects catheterized, 11 (6.6%) experienced acute (day of catheterization) serious adverse events classified as either possibly or definitely related to the procedure, as shown in Table 3. Three subjects experienced an RVOT conduit rupture or dissection, 2 subjects experienced a hemothorax, and 2 subjects had a vessel perforation.

Table 3: Long-term Follow-up PAS: Summary of Acute Procedure-related Serious Adverse Events

Procedure-related Serious Adverse Event	Catheterized Cohort (N=167)
Subjects with procedure-related SAEs	6.6% (11/167)
RVOT conduit rupture or dissection	1.8% (3/167)
Hemothorax	1.2% (2/167)
Perforation of vessel	1.2% (2/167)
Cardiac arrest	0.6% (1/167)
Catheter induced arrhythmia	0.6% (1/167)
Fever (at least 39.0°C)	0.6% (1/167)
Hemorrhage: major	0.6% (1/167)
Ventricular fibrillation	0.6% (1/167)
Vessel dissection	0.6% (1/167)
Other cardiac event	0.6% (1/167)

Procedure-related Serious Adverse Event	Catheterized Cohort (N=167)
Other respiratory/pulmonary	0.6% (1/167)
Other vascular access site complication	0.6% (1/167)

Device-related Adverse Events

Table 4 presents the incidence of device-related adverse events and estimates of the freedom from these events at 1 year, 3 years, and 5 years post-implantation.

Table 4: Long-term Follow-up PAS: Summary of Device-related Adverse Events during Follow-up – Implanted Cohort (N=150)

Event	Subjects with event (n=150)	Freedom from event at 1 year (95% CI[1])	Freedom from event at 3 years (95% CI)	Freedom from event at 5 years (95% CI)
Stent fracture[2] (all)	32.7% (49/150)	82.4% (75.2%, 87.7%)	73.4% (64.8%, 80.2%)	62.0% (48.1%, 73.2%)
Stent fracture: major	15.3% (23/150)	97.3% (92.9, 99.0%)	88.0% (81.0, 92.5%)	84.3% (72.8, 91.2%)
with fragment embolization	0.7% (1/150)	--	--	--
Valve dysfunction: stenosis (all)	18.0% (27/150)	94.6% (89.4%, 97.3%)	85.4% (78.1%, 90.4%)	79.9% (68.1%, 87.7%)
Tricuspid regurgitation	7.3% (11/150)	99.3% (95.2%, 99.9%)	96.5% (91.4%, 98.6%)	91.7% (81.7%, 96.4%)
Prosthetic valve endocarditis	3.3% (5/150)	97.9% (93.7%, 99.3%)	97.2% (92.4%, 99.0%)	96.1% (87.0%, 98.8%)
Valve dysfunction: regurgitation	0.7% (1/150)	100.0% (NA)	100.0% (NA)	99.2% (88.3%, 99.9%)
Paravalvular leak: minor	0.7% (1/150)	99.3% (95.2%, 99.9%)	99.3% (94.6%, 99.9%)	99.3% (87.3%, 100%)
Pulmonary thromboembolism	0.7% (1/150)	100.0% (NA)	99.3% (94.6%, 99.9%)	99.3% (87.5%, 100%)
Valve dysfunction: mixed	0.0% (0/150)	100.0% (NA)	100.0% (NA)	100.0% (NA)
Embolization of the TPV	0.0% (0/150)	100.0% (NA)	100.0% (NA)	100.0% (NA)
Structural deterioration of the TPV	0.0% (0/150)	100.0% (NA)	100.0% (NA)	100.0% (NA)
Non-structural dysfunction	0.0% (0/150)	100.0% (NA)	100.0% (NA)	100.0% (NA)
Paravalvular leak: major	0.0% (0/150)	100.0% (NA)	100.0% (NA)	100.0% (NA)
Thrombosis of the TPV	0.0% (0/150)	100.0% (NA)	100.0% (NA)	100.0% (NA)
Hemorrhage	0.0% (0/150)	100.0% (NA)	100.0% (NA)	100.0% (NA)

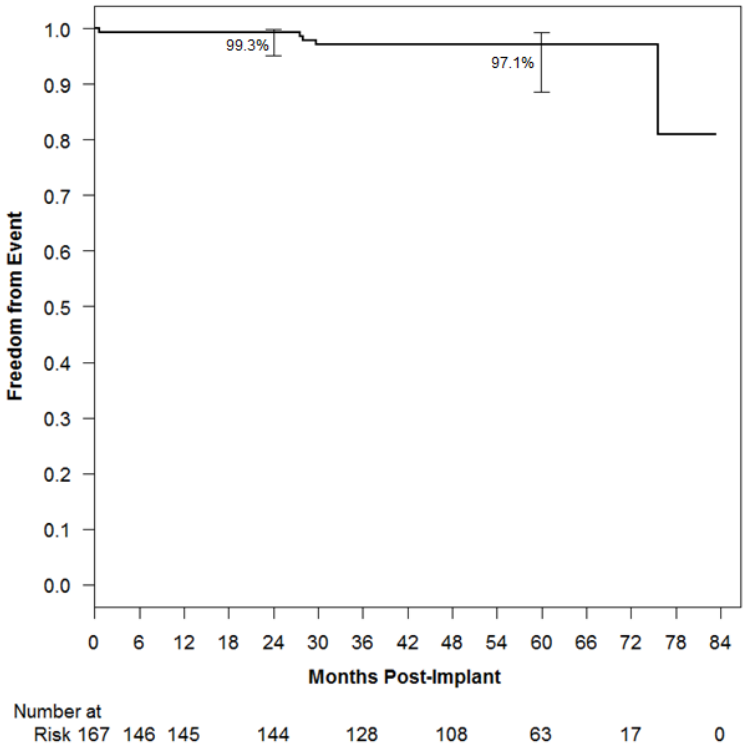
[1] The confidence intervals are calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

[2] The term "stent fracture" refers to the fracture of the Melody TPV. However, in subjects with multiple stents in the RVOT it is difficult to definitively attribute stent fractures to the Melody frame versus another stent.

Freedom from All-cause Mortality

Freedom from all-cause mortality at 5 years post-implantation is estimated to be 97.1%, as shown in Figure 3. There were 5 deaths during follow-up, one of which was early and was reported as possibly related to the procedure. There were 4 late deaths, one of which was reported as possibly device-related.

Figure 3: Kaplan-Meier Freedom from All-cause Mortality – Catheterized Cohort (N=167)



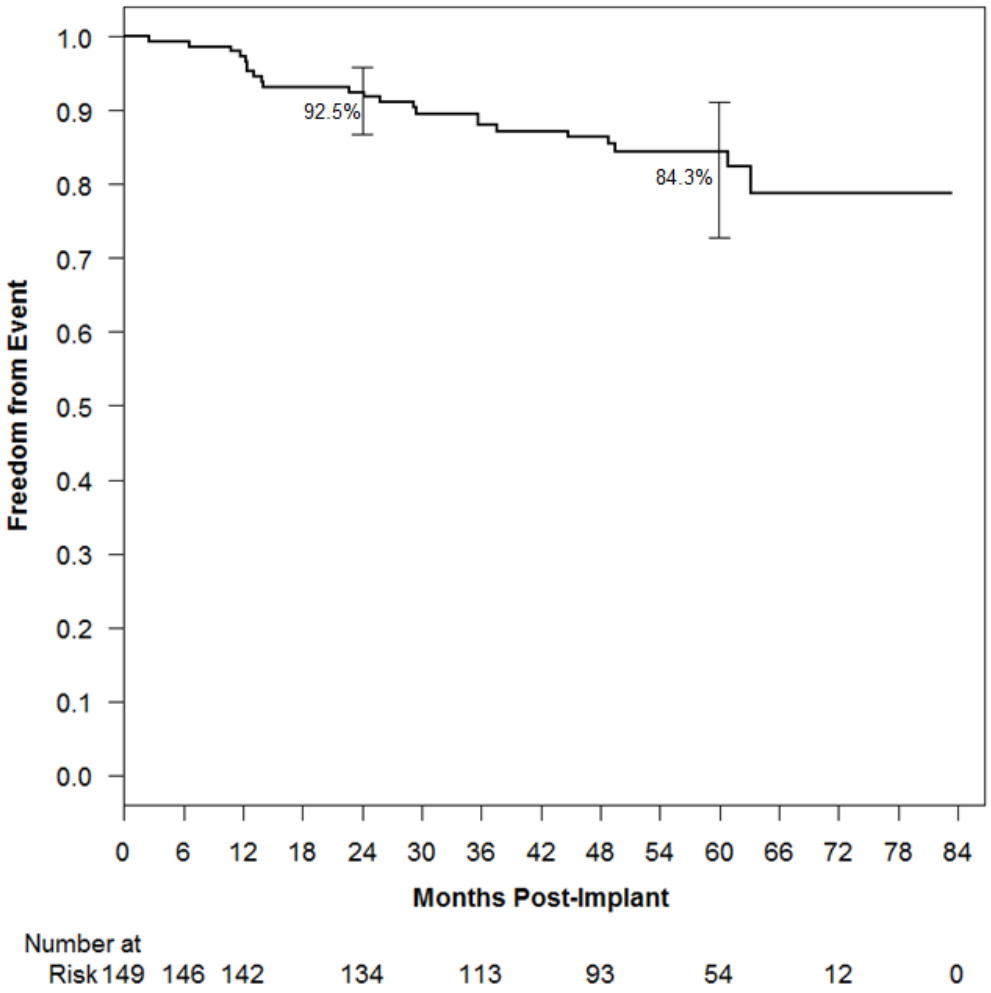
Notes:

1. The cumulative probability of event free estimate is based on the KM method.
2. The 95% confidence interval is the log-log transformed 95% CI using the Peto standard error. The confidence intervals are 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.

Freedom from Major Stent Fracture

Stent fracture was defined as any visual evidence on radiography of loss of contact between elements (cells) of the stent. Major stent fracture includes those where intervention (e.g., reoperation, implantation of another TPV) was required to prevent permanent impairment of a body function or permanent damage to a body structure. Freedom from major stent fracture at 5 years post-implant is estimated to be 84.3%, as shown in Figure 4.

Figure 4: Kaplan-Meier Freedom from Major Stent Fracture – Implanted >24 hours Cohort (N=149)



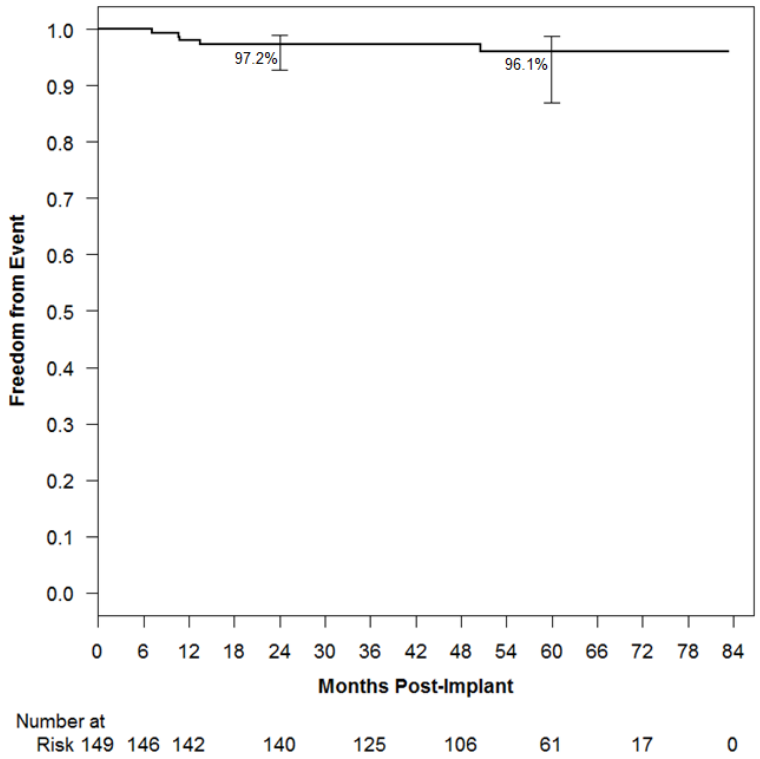
Notes:

1. The cumulative probability of event free estimate is based on the KM method.
2. The 95% confidence interval is the log-log transformed 95% CI using the Peto standard error. The confidence intervals are 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.

Freedom from Prosthetic Valve Endocarditis

Freedom from prosthetic valve endocarditis at 5 years post-implantation is estimated to be 96.1%, as shown in Figure 5. Five subjects were reported to have prosthetic valve endocarditis. Four of the 5 cases were treated with antibiotics, while the TPV was explanted in 1 subject.

Figure 5: Kaplan-Meier Freedom from Endocarditis – Implanted >24 hours Cohort (N=149)



Notes:

1. The cumulative probability of event free estimate is based on the KM method.
2. The 95% confidence interval is the log-log transformed 95% CI using the Peto standard error. The confidence intervals are 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.

3. Effectiveness Results

Procedural Success

Of the 150 subjects with an attempted implant, 94.7% had a procedural success (n=142), as shown in Table 5. All valves delivered remained in the desired implant location; however, one subject was explanted <24 hours after implantation due to conduit rupture, one subject had an RV-PA peak-to-peak gradient >35 mmHg, and 5 subjects had mild or greater PR by angiography. One subject was not assessed for one of the composite variables and thus was considered a procedural failure.

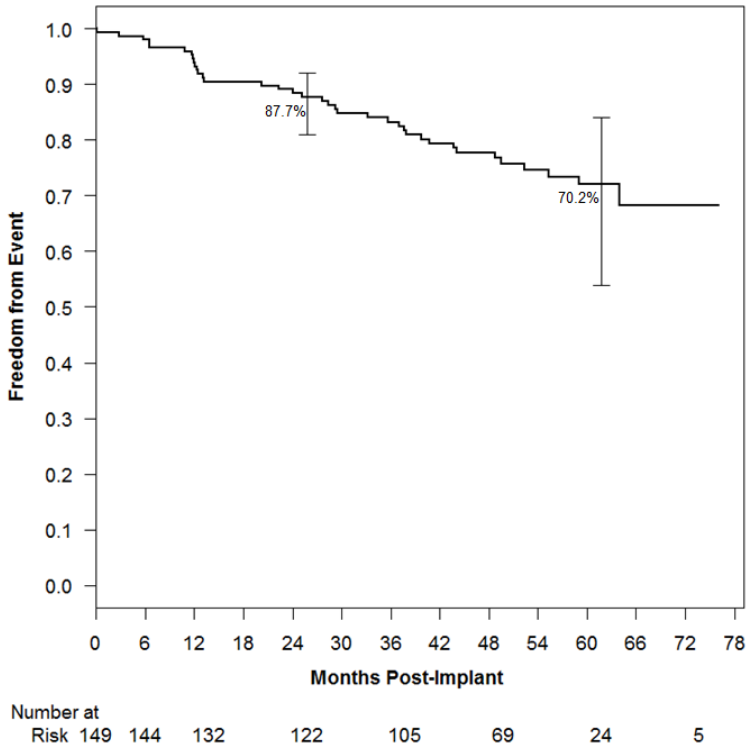
Table 5: Long-term Follow-up PAS: Procedural Success – Attempted Implant Cohort (N=150)

	Attempted Implant Cohort (N=150)
Number of subjects attempted	150
Number of subjects with procedural success	142
Percent of subjects with procedural success	94.7%

Freedom from TPV Dysfunction

At 5 years, the freedom from TPV dysfunction (as defined above) is estimated to be 72.0%, as shown in Figure 6. Of the 37 subjects with TPV dysfunction throughout follow-up, 34 presented with stenosis, most often secondary to stent fracture. Two subjects presented with moderate PR during follow-up that did not require intervention, and 1 subject was explanted due to heart failure and the need for a right ventricular assist device.

Figure 6: Kaplan-Meier Freedom from TPV Dysfunction – Implanted >24 hours Cohort (N=149)



Notes:

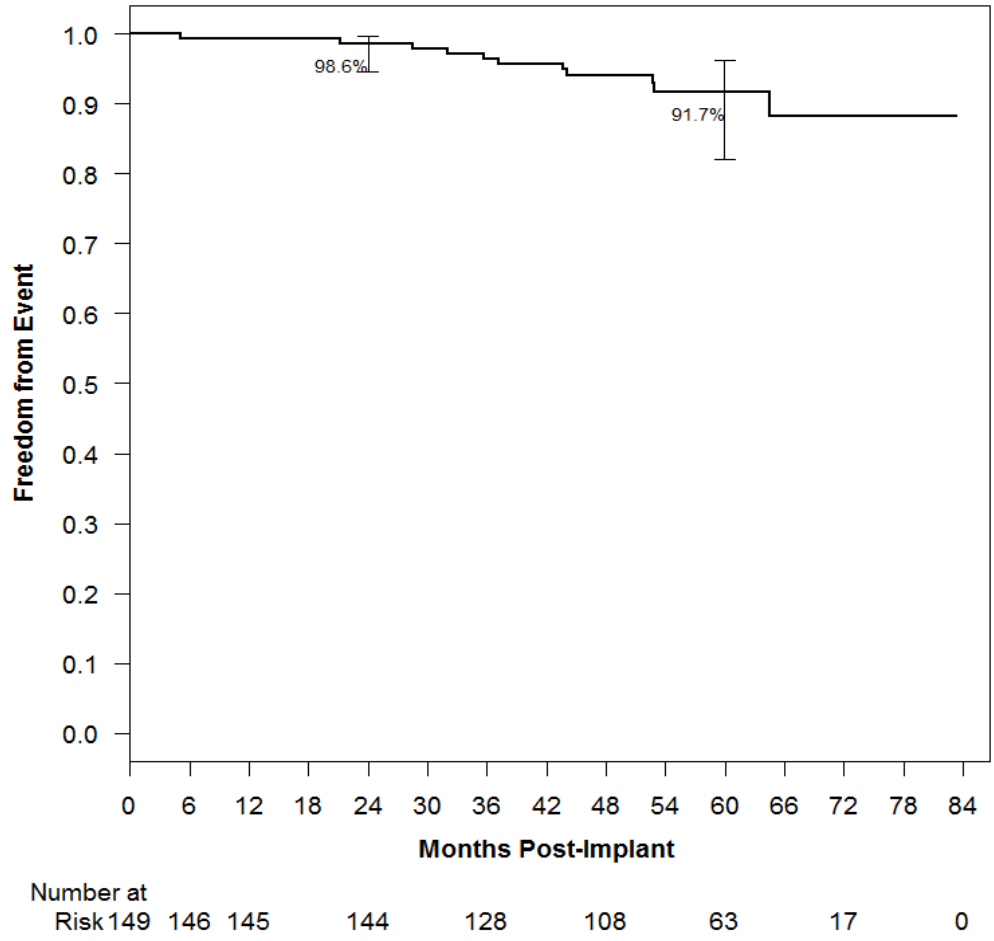
1. The cumulative probability of event free estimate is based on the KM method.
2. The 95% confidence interval is the log-log transformed 95% CI using the Peto standard error. The confidence intervals are calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.
3. Since TPV dysfunction is a composite outcome relying on echocardiographic assessment at each visit interval, the K-M rate at the end of the visit window is presented.

Freedom from RVOT Conduit Reoperation

At 5 years post-implantation, the freedom from RVOT conduit reoperation is estimated to be 91.7%, as shown in Figure 7. Eleven subjects underwent RVOT conduit reoperation during follow-up. The indication for reoperation was stenosis in 9 subjects, endocarditis in 1 subject, and heart failure with the need for a right

ventricular assist device in 1 subject. Of the subjects who were explanted, 2 had been previously treated with a second Melody TPV and 2 had been treated with balloon angioplasty of the index Melody TPV prior to surgical explant.

Figure 7: Kaplan-Meier Freedom from RVOT Conduit Reoperation – Implanted >24 hours Cohort (N=149)



Notes:

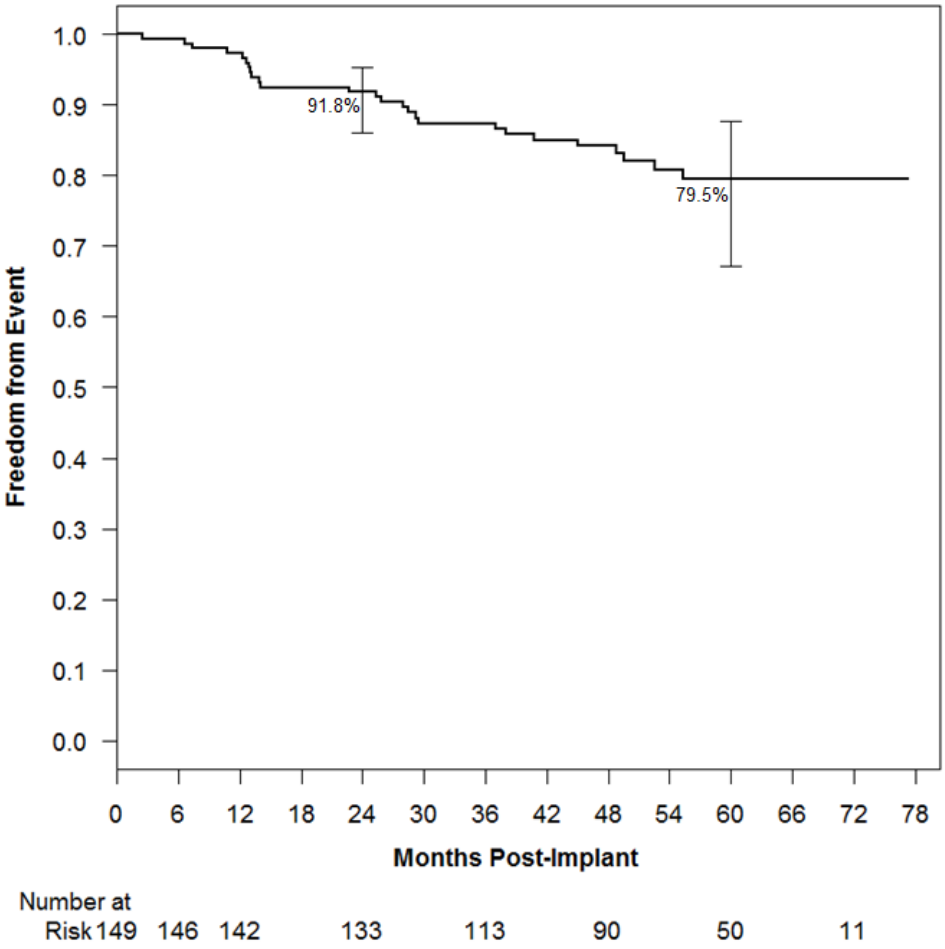
1. The cumulative probability of event free estimate is based on the KM method.
2. The 95% confidence interval is the log-log transformed 95% CI using the Peto standard error. The confidence intervals are calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Freedom from Catheter Re-intervention on the TPV

Freedom from catheter re-intervention at 5 years post-implantation is estimated to be 79.5%, as shown in Figure 8. The most common reason for re-intervention was stenosis. Twenty subjects received a subsequent Melody TPV, with or without stenting; one of these subjects went on to receive a third Melody TPV, while 2 others were subsequently explanted. Five subjects underwent balloon angioplasty of the index Melody TPV. One subject underwent stenting of the TPV to treat

stenosis; the TPV was subsequently explanted because of clinically significant PR.

Figure 8: Kaplan-Meier Freedom From Catheter Re-intervention on the TPV – Implanted >24 hours Cohort (N=149)



Notes:

1. The cumulative probability of event free estimate is based on the KM method.
2. The 95% confidence interval is the log-log transformed 95% CI using the Peto standard error. The confidence intervals are 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.

Hemodynamic Performance

At discharge and throughout 5 years of follow-up, the majority of subjects had no more than mild PR, as shown in Table 6. Two subjects presented with moderate PR during follow-up, and no subjects presented with severe PR.

Table 6: Long-term Follow-up PAS: Pulmonary Regurgitation by Time Interval – Implanted >24 hours Cohort (N=149)

Degree of Regurgitation[1,2]	Pre-Implant (n=149)	Discharge (n=148)	3 Months (n=146)	6 Months (n=143)	1 Year (n=142)	2 Years (n=137)	3 Years (n=119)	4 Years (n=105)	5 Years (n=66)
None	5.5% (8/146)	71.7% (104/145)	75.5% (108/143)	76.3% (106/139)	79.1% (110/139)	70.7% (94/133)	69.6% (78/112)	73.2% (71/97)	70.0% (42/60)
Trace	3.4% (5/146)	24.8% (36/145)	19.6% (28/143)	20.9% (29/139)	14.4% (20/139)	22.6% (30/133)	23.2% (26/112)	19.6% (19/97)	16.7% (10/60)
Mild	12.3% (18/146)	3.4% (5/145)	4.9% (7/143)	2.9% (4/139)	5.8% (8/139)	6.8% (9/133)	7.1% (8/112)	6.2% (6/97)	13.3% (8/60)
Moderate	30.8% (45/146)	0.0% (0/145)	0.0% (0/143)	0.0% (0/139)	0.7% (1/139)	0.0% (0/133)	0.0% (0/112)	1.0% (1/97)	0.0% (0/60)
Severe	47.9% (70/146)	0.0% (0/145)	0.0% (0/143)	0.0% (0/139)	0.0% (0/139)	0.0% (0/133)	0.0% (0/112)	0.0% (0/97)	0.0% (0/60)

[1] Table includes data from subjects who have undergone implantation of a subsequent Melody TPV as applicable.
[2] Pulmonary regurgitation was unable to be assessed for 3 subjects pre-implant, 3 subjects at discharge, 3 subjects at 3 months, 4 subjects at 6 months, 3 subjects at 1 year, 4 subjects at 2 years, 7 subjects at 3 years, 8 subjects at 4 years, and 6 subjects at 5 years post-implant.

The average RVOT mean gradient was 17.7 ± 7.7 mmHg at discharge and remained clinically stable throughout follow-up, as shown in Table 7.

Table 7: Long-term Follow-up PAS: RVOT Mean Gradient by Time Interval – Implanted >24 hours Cohort (N=149)

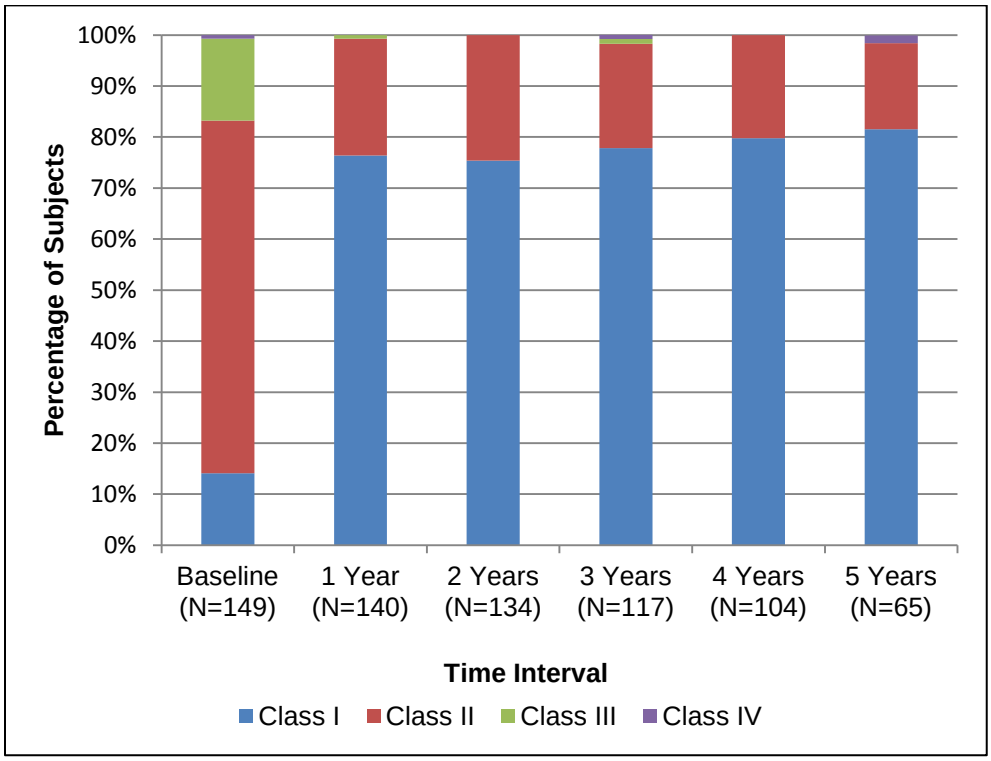
RVOT Mean Gradient[1,2]	Pre-Implant (n=149)	Discharge (n=148)	3 Months (n=146)	6 Months (n=143)	1 Year (n=142)	2 Years (n=137)	3 Years (n=119)	4 Years (n=105)	5 Years (n=66)
n	147	147	145	142	140	136	116	100	63
Mean ± SD	32.1±13.9	17.7±7.7	17.5±7.9	17.6±7.6	18.7±9.1	17.6±10.0	17.5±7.8	18.2±8.5	17.1±7.5
Median [Min, Max]	32.0 [5.2, 97.0]	17.0 [3.4, 51.0]	17.0 [4.0, 53.0]	16.0 [5.0, 48.0]	17.0 [4.0, 51.0]	15.5 [4.0, 72.0]	16.0 [4.0, 41.1]	16.5 [4.0, 47.0]	16.0 [4.2, 40.1]
Q1, Q3	21.0, 40.8	12.0, 22.0	13.0, 20.0	12.6, 21.0	12.0, 23.0	11.0, 22.0	12.0, 22.0	12.0, 24.0	12.0, 22.0

[1] Table includes data from subjects who have undergone implantation of a subsequent Melody TPV as applicable.
[2] RVOT mean gradient was unable to be assessed for 2 subjects pre-implant, 1 subject at discharge, 1 subject at 3 months, 1 subject at 6 months, 2 subjects at 1 year, 1 subject at 2 years, 3 subjects at 3 years, 5 subjects at 4 years, and 3 subjects at 5 years post-implant.

NYHA

Figure 9 presents the NYHA functional class of subjects throughout follow-up. Pre-implantation, the majority of patients were NYHA Class II. Following Melody TPV implantation and throughout follow-up, the majority of subjects were in class I.

Figure 9: New York Heart Association Classification – Implanted >24 hours Cohort (N=149)



X.2. Melody TPV New Enrollment PAS

A. Study Design

Following HDE approval of the Melody TPV in 2010, a New Enrollment PAS was initiated at 10 new centers in the United States. It is a prospective, non-randomized, multi-center study designed to demonstrate that the short-term (6-months) hemodynamic function of the Melody TPV achieved by non-IDE investigators and centers is similar to the historical control established by the results of the 5-center IDE study.

The New Enrollment PAS utilized an independent core echocardiography laboratory for all subjects enrolled through at least their 6 month follow-up exams, and continues to use an independent core pathology laboratory to analyze explanted devices.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the New Enrollment PAS was limited to patients who met the following inclusion criteria:

   - Existence of a full (circumferential) RVOT conduit ≥ 16 mm in diameter when originally implanted, and

- Dysfunctional RVOT conduits with a clinical indication for intervention, and:
    - Regurgitation: ≥ moderate regurgitation, and/or
    - Stenosis: mean RVOT gradient ≥ 35 mmHg

Patients were <u>not</u> permitted to enroll in in the New Enrollment PAS if they met any of the following exclusion criteria:

- Implant in the aortic or mitral position
- Venous anatomy unable to accommodate a 22-fr size introducer sheath
- Obstruction of the central veins
- Clinical or biological signs of infection including active endocarditis
- Unwilling or unable to provide written informed consent or comply with the follow-up requirements

2. <u>Follow-up Schedule</u>
   The follow-up schedule and associated clinical evaluations are as follows:
    - Discharge
        - Clinical assessment (NYHA not assessed at discharge)
        - Transthoracic echocardiogram (TTE)
        - Chest radiography
    - 6 months
        - Clinical assessment
        - TTE
        - Fluoroscopy
    - 1 year
        - Clinical assessment
        - TTE
        - Chest radiography
    - 2-5 years: annually
        - Clinical assessment
        - TTE (if visit is at study center)
        - Chest radiography (if visit is at study center)

3. <u>Clinical outcomes</u>
   The primary outcome measure is acceptable TPV hemodynamic function at 6 months after successful TPV implantation, which is a composite outcome defined as mean RVOT gradient ≤ 30 mmHg as measured by CW Doppler, severity of PR less than moderate by Doppler echocardiography, and freedom from RVOT conduit reoperation and catheter re-intervention at 6 months.
   Secondary safety and effectiveness outcome measures include:
    (1) Percent of subjects with procedural success
    (2) Percent of subjects with serious procedural adverse events
    (3) Percent of subjects with serious device-related adverse events post-implantation
    (4) Freedom from stent fracture
    (5) Freedom from re-intervention on the TPV

(6) Freedom from RVOT conduit reoperation
(7) Freedom from death (all-cause, procedural, and device-related)
(8) Changes in NYHA functional classification

Longer-term (5-year) follow-up of enrolled patients was pre-specified for the secondary outcome measures.

4. Accountability of Study Subjects

A total of 131 subjects were enrolled in this study between July 29, 2010 and July 12, 2012. In total, 120 subjects (92%) underwent catheterization for potential implantation of the Melody TPV; of these, 101 subjects had an implant attempt, and 100 subjects (83% of catheterized subjects) received the valve.

B. Study Population Demographics and Baseline Parameters

Table 8 presents the subject demographics and baseline characteristics for the enrolled subjects. The study population consisted of 87 male and 44 female subjects with a mean age of 20.1 ± 9.8 (range 5 to 50 years). Tetralogy of Fallot was the most common original diagnosis (36.6%) followed by aortic valve disease in subjects having undergone a Ross procedure (16.8%). Homografts were the most common target for Melody TPV implantation.

Table 8: New Enrollment PAS: Subject Demographics / Baseline Data – Enrolled Cohort (N=131)

Assessment	Enrolled Cohort (N=131)
Gender	
Male	66.4% (87/131)
Female	33.6% (44/131)
Age (years)	
N	131
Mean ± SD	20.1 ± 9.8
Median [Min, Max]	17.0 [5.0, 50.0]
Original diagnosis	
Tetralogy of Fallot	36.6% (48/131)
Aortic valve disease (Ross)	16.8% (22/131)
Isolated pulmonary stenosis	3.8% (5/131)
Truncus arteriosus	15.3% (20/131)
Transposition of the great arteries	7.6% (10/131)
Double outlet right ventricle	7.6% (10/131)
Other[1]	12.2% (16/131)
RVOT conduit type	
Homograft	66.4% (87/131)
Biological valved conduit	19.1% (25/131)
Bioprosthesis	13.0% (17/131)
Synthetic	1.5% (2/131)
Other	0.0% (0/131)
RVOT conduit size (mm)	
N	113

Assessment	Enrolled Cohort (N=131)
Mean ± SD	20.9 ± 3.4
Median [Min, Max]	21.0 [8.0, 30.0]
Bioprosthesis size (mm)	
N	17
Mean ± SD	24.5 ± 3.1
Median [Min, Max]	25.0 [19.0, 31.0]

[1] Other original diagnosis include: pulmonary atresia with ASD and/or VSD (n=3); pulmonary atresia with intact ventricular septum (n=2); pulmonary stenosis with atrial septal defect and/ or VSD (n=2); TOF with hypoplastic pulmonary arteries and pulmonary annulus (n=1); TOF with coronary artery anomalies (n=1); TOF with complete atrio-ventricular canal (n=1); aortopulmonary window (n=1); interrupted aortic arch, ASD, and VSD (n=1); coarctation of the aorta with VSD (n=1); interrupted aortic arch with VSD (n=1); aortic and sub-aortic stenosis (n=1); situs ambiguus asplenia, dextrocardia, and AV canal (n=1).

C. Safety and Effectiveness Results

Data presented herein are interim results through March 1, 2014. The mean length of follow-up was 25.1 ± 9.4 months.

1. Procedural Data

A summary of procedural data is provided in Table 9. The percutaneous femoral venous approach was used in the majority of subjects (88.3%); however, in some patients, internal jugular vein access was used (11.7%). The protocol for the study also permitted concomitant procedures, including pre-stenting. As with the IDE study cohort, no particular number or types of stents were specified in the protocol, nor were there specified criteria for performing the pre-stenting procedure. The majority of subjects (75.8%) underwent concomitant procedures; pre-stenting of the RVOT was the most common concomitant procedure, occurring in 65.8% of the catheterized patients. The mean length of hospital stay was 1.3 ± 2.8 days.

Table 9: New Enrollment PAS: Procedural Data – Catheterized Cohort (N=120)

Assessment[1]	Catheterized Cohort (N=120)
Venous Site Access	
Femoral vein	88.3% (106/120)
Jugular vein	11.7% (14/120)
Subclavian vein	0.0% (0/120)
Concomitant procedures[2]	
No concomitant procedures	24.2% (29/120)
Stent placement, peripheral PA	7.5% (9/120)
Balloon angioplasty, peripheral PA	10.8% (13/120)
Stent placement, RVOT conduit	65.8% (79/120)
Placement of intravascular coil	0.0% (0/120)
Closure of ASD or PFO	0.0% (0/120)
Closure of VSD	0.0% (0/120)
Other[3]	8.3% (10/120)
Length of hospital stay (days)	

Assessment[1]	Catheterized Cohort (N=120)
n	120
Mean ± SD	1.3 ± 2.8
Median [Min, Max]	1.0 [0.0, 31.0]

[1] Fluoroscopy time was not collected per the PAS protocol (as presented in the IDE and PMSS procedural data tables).
[2] Subjects may have had more than one concomitant procedure performed.
[3] Other concomitant procedures included: balloon angioplasty of conduit (n=5), dilation of LPA or RPA stents (n=2), balloon angioplasty of the proximal LPA (n=1), left ventricular assist device placed (n=1), pulmonary valvuloplasty (n=1).

2. Safety Results

Acute Procedure-related Adverse Events

Of the 120 subjects catheterized, 10 (8.3%) experienced an acute (day of catheterization) serious adverse events classified by the investigator as either possibly or definitely related to the procedure, as shown in Table 10. Five subjects experienced an RVOT conduit rupture or dissection, all of which were managed by clinicians with the implantation of a covered stent. The rate of procedure-related serious adverse events was higher in the New Enrollment PAS (8.3%) than in the Long-term Follow-up PAS (6.6%), predominantly due to a higher rate of RVOT conduit rupture or dissection in the New Enrollment PAS (4.2% versus 1.8%).

Table 10: New Enrollment PAS: Summary of Procedure-related Serious Adverse Events – Catheterized Cohort (N=120)

Procedure-related Serious Adverse Event	Catheterized Cohort (N=120)
Subjects with procedure-related SAEs	8.3% (10/120)
RVOT conduit rupture or dissection	4.2% (5/120)
Catheter induced arrhythmia	0.8% (1/120)
Coronary compression causing myocardial ischemia	0.8% (1/120)
Paravalvular leak: major	0.8% (1/120)
Perforation of vessel	0.8% (1/120)
Pseudoaneurysm	0.8% (1/120)
Valve dysfunction: regurgitation	0.8% (1/120)
Other central nervous system	0.8% (1/120)
Other implantation/catheterization	0.8% (1/120)
Other respiratory/pulmonary	0.8% (1/120)

Device-related Adverse Events

Table 11 presents the current incidence of device-related adverse events and estimates of the freedom from such events at 1 year and 2 years post-implantation. Compared to the Long-term Follow-up PAS, the incidence to date of major stent fracture is lower in the New Enrollment PAS (4.0% versus 15.3%), whereas the incidence to date of prosthetic valve endocarditis in the New Enrollment PAS is higher (7.0% versus 3.3%).

Table 11: New Enrollment PAS: Summary of Device-related Adverse Events during Follow-up – Implanted Cohort (N=100)

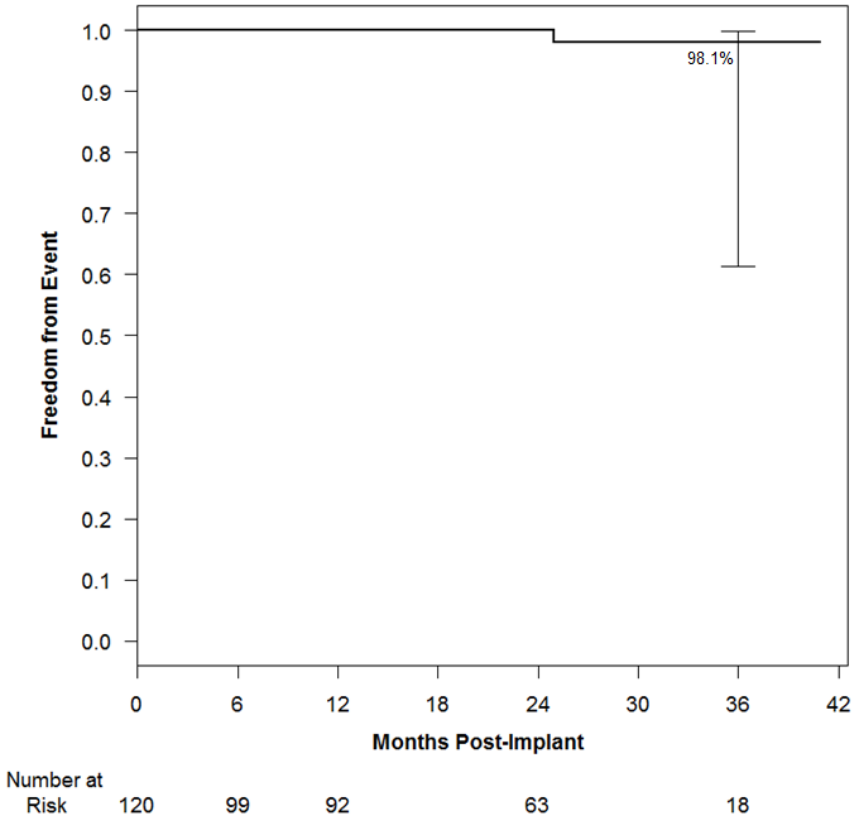
Event	Subjects with event (n=100)	Freedom from event at 1 year (95% CI[1])	Freedom from event at 2 years (95% CI)
Stent fracture[2] (all)	15.0% (15/100)	90.7% (82.7%, 95.2%)	87.0% (76.0%, 93.1%)
Stent fracture: major	4.0% (4/100)	99.0% (92.5%, 99.9%)	97.6% (88.9%, 99.5%)
with fragment embolization	1.0% (1/100)	--	--
Valve dysfunction: stenosis (all)	9.0% (9/100)	99.0% (92.5%, 99.9%)	96.3% (87.6%, 99.0%)
Prosthetic valve endocarditis	7.0% (7/100)	97.0% (90.5%, 99.0%)	92.9% (83.2%, 97.1%)
Valve dysfunction: regurgitation	4.0% (4/100)	98.0% (91.7%, 99.5%)	96.7% (87.6%, 99.1%)
Valve dysfunction: mixed	2.0% (2/100)	100.0% (NA)	98.4% (89.3%, 99.8%)
Structural deterioration of the TPV[3]	1.0% (1/100)	100.0% (NA)	100.0% (NA)
Paravalvular leak: minor	1.0% (1/100)	99.0% (92.5%, 99.9%)	99.0% (88.8%, 99.9%)
Paravalvular leak: major	1.0% (1/100)	99.0% (92.4%, 99.9%)	99.0% (88.7%, 99.9%)
Pulmonary thromboembolism	1.0% (1/100)	99.0% (92.5%, 99.9%)	99.0% (88.8%, 99.9%)
Valvular regurgitation, tricuspid[2]	1.0% (1/100)	100.0% (NA)	100.0% (NA)
Embolization of the TPV	0.0% (0/100)	100.0% (NA)	100.0% (NA)
Non-structural dysfunction	0.0% (0/100)	100.0% (NA)	100.0% (NA)
Thrombosis of the TPV	0.0% (0/100)	100.0% (NA)	100.0% (NA)
Hemorrhage	0.0% (0/100)	100.0% (NA)	100.0% (NA)

[1] The confidence intervals are 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.
[2] The term "stent fracture" refers to the fracture of the Melody TPV. However, in subjects with multiple stents in the RVOT it is difficult to definitively attribute stent fractures to the Melody frame versus another stent.
[3] These events occurred after 2 years.

Freedom from All-cause Mortality

Freedom from all-cause mortality at 3 years post-implantation is estimated to be 98.1%%, as shown in Figure 10. There was 1 death during follow-up that occurred more than 2 years post-implantation. The cause of death (autopsy) was bacterial endocarditis with septic emboli, while the investigator-reported cause of death was arrhythmia.

Figure 10: Kaplan-Meier Freedom from All-cause Mortality – Catheterized Cohort (N=120)



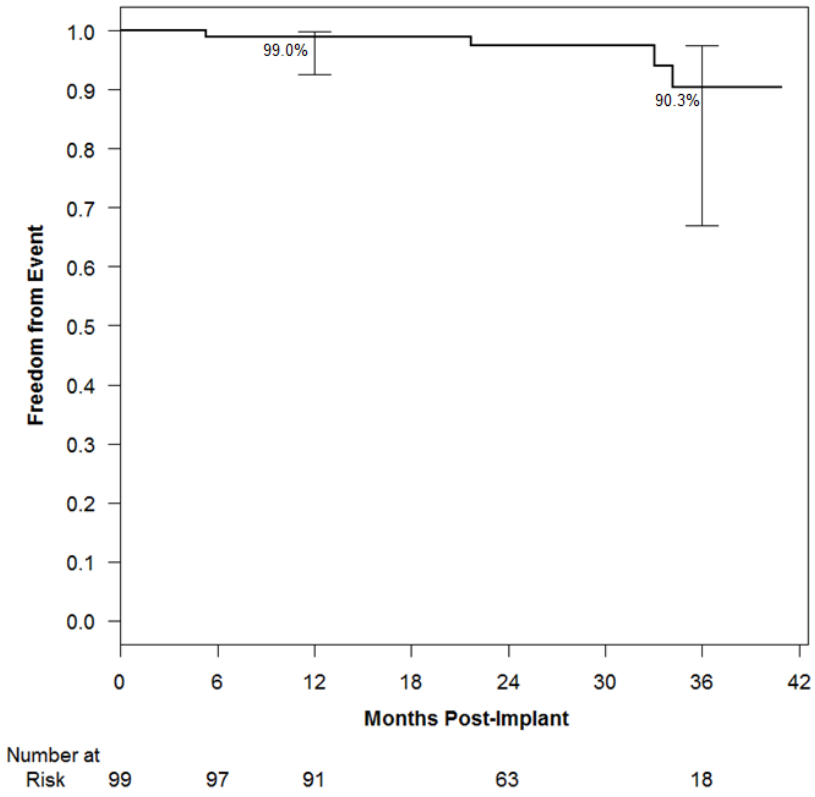
Notes:

1. The cumulative probability of event free estimate is based on the KM method.
2. The 95% confidence interval is the log-log transformed 95% CI using the Peto standard error. The confidence interval is provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Freedom from Major Stent Fracture

Freedom from major stent fracture at 3 years post-implantation is estimated to be 90.3%, as shown in Figure 11.

Figure 11: Kaplan-Meier Freedom From Major Stent Fracture – Implanted >24 hours Cohort (N=99)



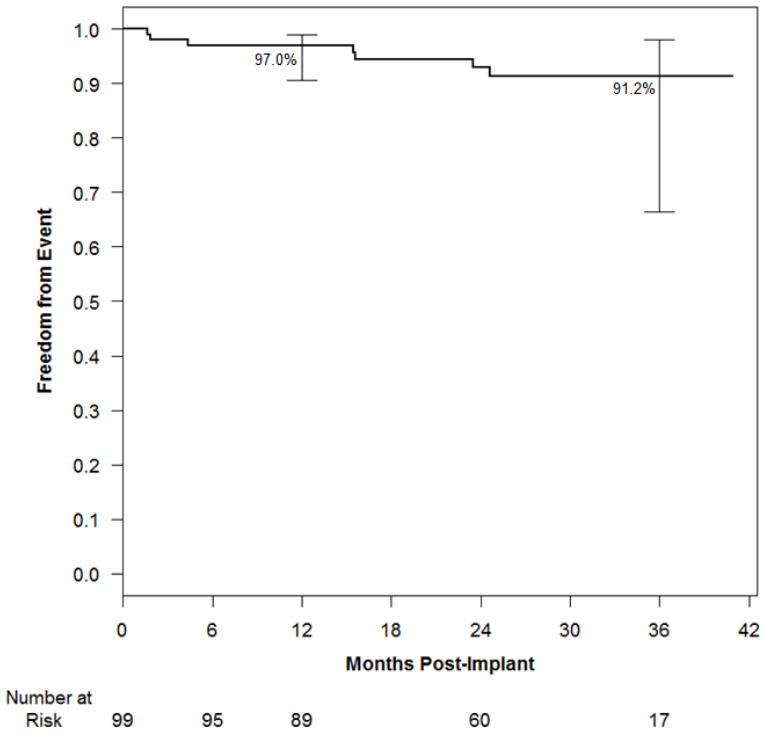
Notes:

1. The cumulative probability of event free estimate is based on the KM method.
2. The 95% confidence interval is the log-log transformed 95% CI using the Peto standard error. The confidence intervals are 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.

Freedom from Prosthetic Valve Endocarditis

Freedom from prosthetic valve endocarditis at 3 years post-implantation is estimated to be 91.2%, as shown in Figure 12. Seven subjects were reported to have prosthetic valve endocarditis. Three of the 7 cases were treated with antibiotics, three had the TPV explanted, and 1 subject died 10 days after endocarditis was diagnosed.

Figure 12: Kaplan-Meier Freedom From Prosthetic Valve Endocarditis – Implanted >24 hours Cohort (N=99)



Notes:

1. The cumulative probability of event free estimate is based on the KM method.
2. The 95% confidence interval is the log-log transformed 95% CI using the Peto standard error. The confidence intervals are 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.

3. Effectiveness Results

Procedural Success

Of the 101 subjects with an attempted implantation, 93 (92.1%) had a procedural success (Table 12). Implantation was aborted in 1 subject due to distal branch pulmonary artery perforation leading to pulmonary hemorrhage, which resolved on its own. All valves delivered remained in the desired implant location; however, 1 subject was explanted <24 hours after implant due to occlusion of the left coronary artery. Six subjects had mild PR by angiography immediately after TPV implantation.

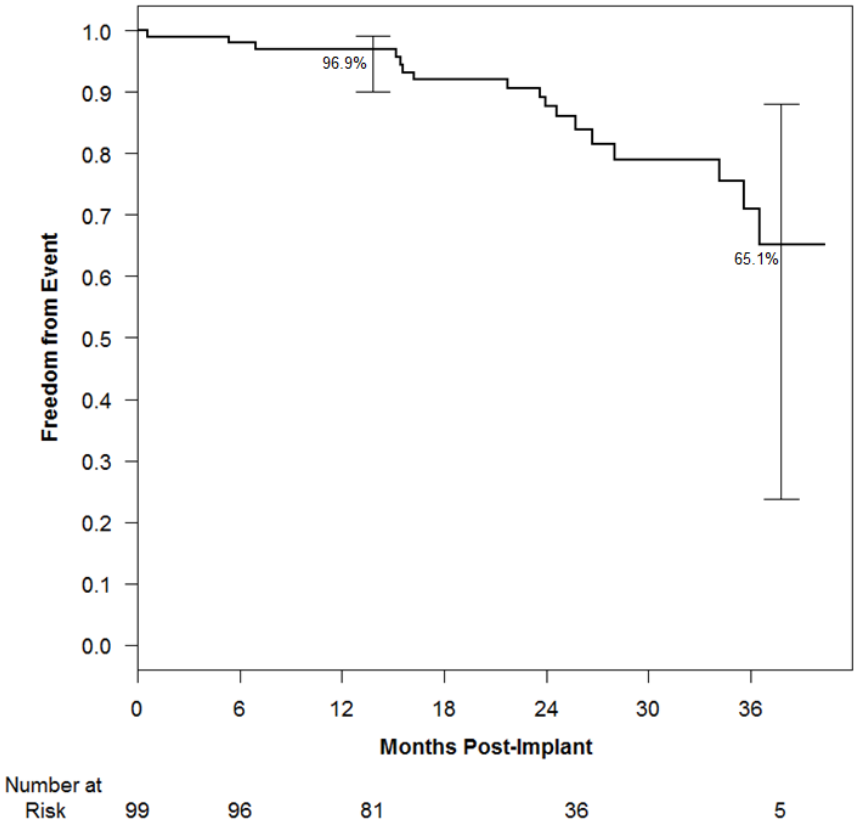
Table 12: New Enrollment PAS: Procedural Success – Attempted Implant Cohort (N=101)

Variable	Attempted Implant Cohort (N=101)
Number of subjects attempted	101
Number of subjects with procedural success	93
Percent of subjects with procedural success	92.1%

Freedom from TPV Dysfunction

At 3 years, the freedom from TPV dysfunction (as defined above) is estimated to be 65.1%, as shown in Figure 13. Of the 17 subjects with TPV dysfunction throughout follow-up, 13 presented with stenosis: 6 secondary to Melody stent fracture, 4 recurrent, and 3 secondary to endocarditis. Three subjects presented with moderate PR during follow-up that did not require intervention, and 1 subject had the RVOT conduit replaced while undergoing aortic valve replacement.

Figure 13: Kaplan-Meier Freedom from TPV Dysfunction – Implanted >24 hours Cohort (N=99)



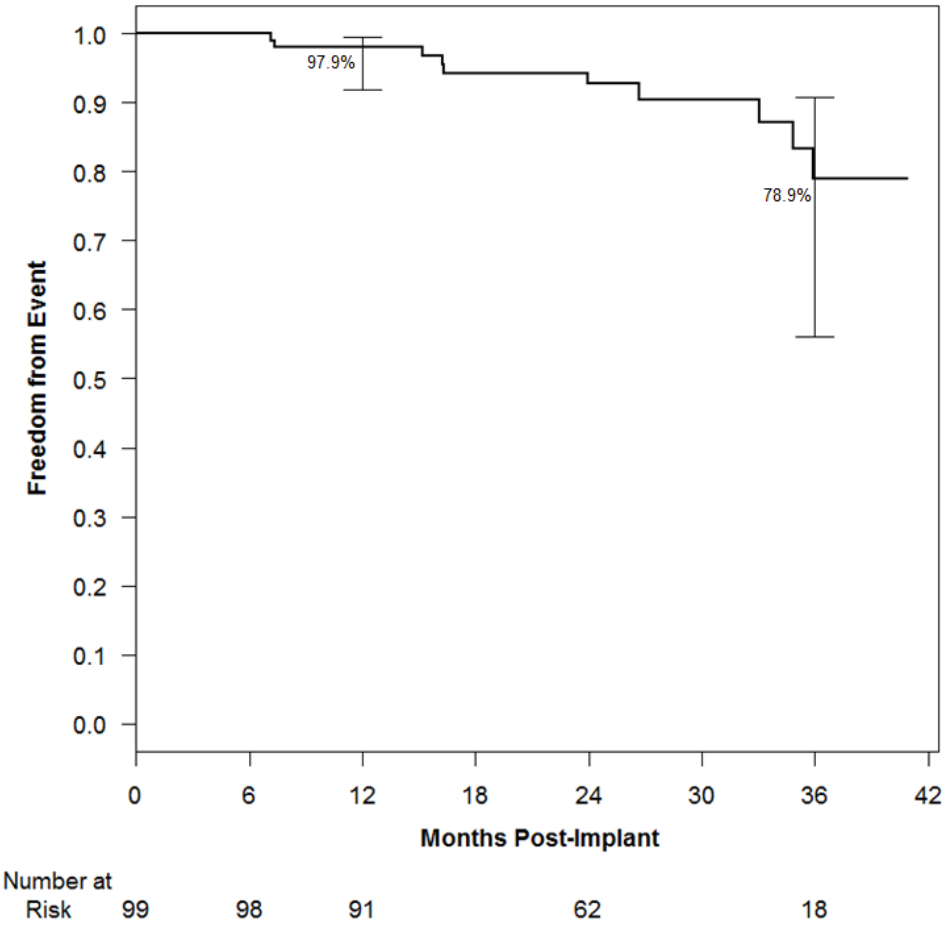
Notes:

1. The cumulative probability of event free estimate is based on the KM method.
2. The 95% confidence interval is the log-log transformed 95% CI using the Peto standard error. The confidence intervals are 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.
3. Since TPV dysfunction is a composite outcome relying on echocardiographic assessment at each visit interval, the K-M rate at the end of the visit window is presented.

Freedom from RVOT Conduit Reoperation

At 3 years post-implantation, the freedom from RVOT conduit reoperation was estimated to be 78.9%, as shown in Figure 14. Ten subjects underwent RVOT conduit reoperation during follow-up. The indication for reoperation was stenosis secondary to stent fracture in 4 subjects, endocarditis in 3 subjects, recurrent stenosis in 2 subjects, and RVOT replacement during aortic valve replacement in 1 subject. One subject with recurrent stenosis had undergone balloon angioplasty prior to surgical explant.

Figure 14: Kaplan-Meier Freedom from RVOT Conduit Reoperation – Implanted >24 hours Cohort (N=99)



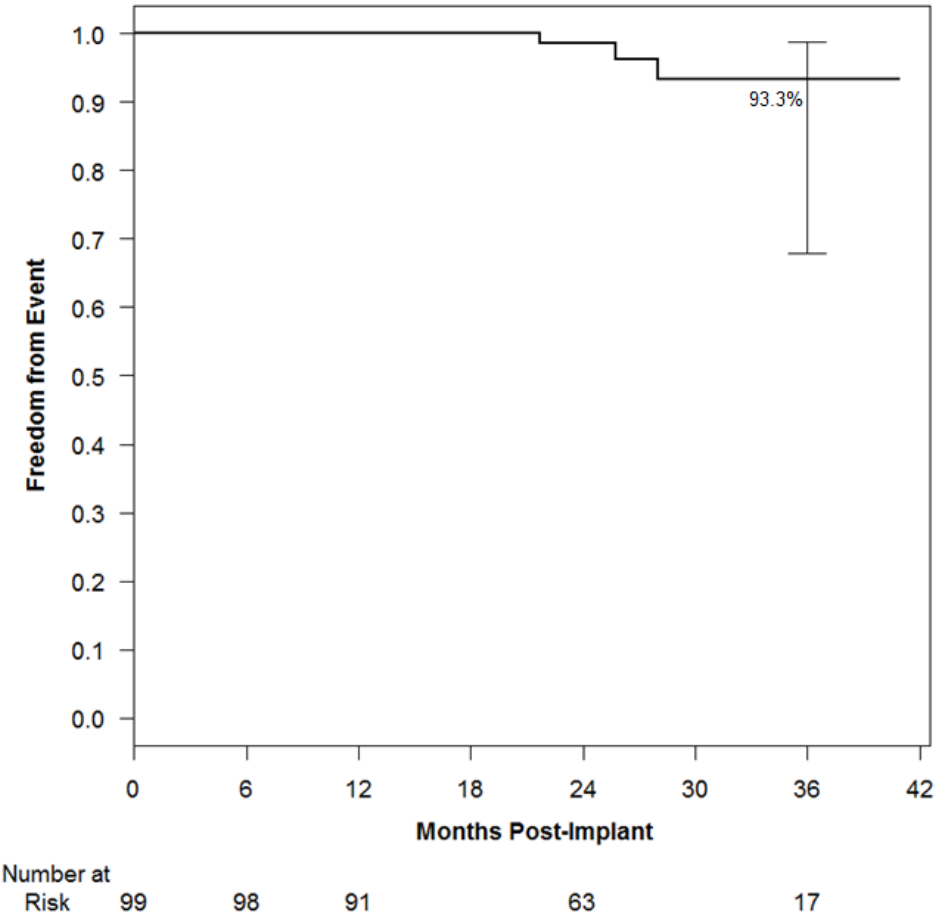
Notes:

1. The cumulative probability of event free estimate is based on the KM method.
2. The 95% confidence interval is the log-log transformed 95% CI using the Peto standard error. The confidence intervals are 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.

Freedom from Catheter Re-intervention on the TPV

Freedom from catheter re-intervention at 3 years post-implantation is estimated to be 93.3%, as shown in Figure 15. During follow-up, 3 subjects had a catheter re-intervention performed on the Melody TPV. One subject had a second Melody TPV implanted for stenosis secondary to stent fracture and 1 subject underwent balloon angioplasty for recurrent stenosis. Additionally, 1 subject underwent balloon angioplasty for stenosis secondary to stent fracture, but this TPV was later explanted.

Figure 15: Kaplan-Meier Freedom from Catheter Re-intervention on the TPV – Implanted >24 hours Cohort (N=99)



Notes:

1. The cumulative probability of event free estimate is based on the KM method.
2. The 95% confidence interval is the log-log transformed 95% CI using the Peto standard error. The confidence interval is provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Primary Outcome Measure

The primary objective of the New Enrollment PAS is to confirm the short-term hemodynamic effectiveness of implantation of the Melody TPV achieved by real-world providers is equivalent to the historical control established in the five-center IDE study (75%).

Of the 99 subjects that were implanted greater than 24 hours, 3 subjects did not have acceptable TPV hemodynamic function at 6 months as they had a mean RVOT gradient above 30 mmHg. The TPV hemodynamic function at 6 months was unable to be evaluated for 9 subjects: one subject withdrew after hospital discharge; one subject did not have the 6-month echo test; 7 subjects did not have the 6-month mean gradient and TPV regurgitation measurements.

The primary objective was met with 96.7% (p-value < 0.0001) of subjects having acceptable hemodynamic function at 6 months after the Melody TPV implant. The primary objective was also met for the best-case and worst-case analyses. Results are presented in Tables 13-15.

Table 13: New Enrollment PAS: Acceptable Hemodynamic Function at 6 Months Postoperative – Implanted >24 hours Cohort (N=99)
(Excluding the Subjects Whose Echo Data were not Evaluable)

Number of Subjects in the Analysis	Number and percentage of subjects with acceptable TPV hemodynamic function	Standard Error for Percentage	One-sided 95% Lower Confidence Bound	Hypothesis Testing	
90	87 (96.7%)	1.9%	91.6%	p-value	Objective Met
				<0.0001	Yes

Note: The p-value was from the exact test.

Table 14: New Enrollment PAS: Subjects with Acceptable Hemodynamic Function at 6 Months Postoperative – Implanted >24 hours Cohort (N=99) – Worst Case
(Assuming All Unable-to-be-assessed Cases Were Failures)

Number of Subjects in the Analysis	Number and percentage of subjects with acceptable TPV hemodynamic function	Standard Error for Percentage	One-sided 95% Lower Confidence Bound	Hypothesis Testing	
99	87 (87.9%)	3.3%	81.1%	p-value	Objective Met
				0.0012	Yes

Note: The p-value was from the exact test.

Table 15: New Enrollment PAS: Subjects with Acceptable Hemodynamic Function at 6 Months Postoperative – Implanted >24 hours Cohort (N=99) – Best Case (Assuming All Unable-to-be-assessed Cases Were Successes)

Number of Subjects in the Analysis	Number and percentage of subjects with acceptable TPV hemodynamic function	Standard Error for Percentage	One-sided 95% Lower Confidence Bound	Hypothesis Testing	
				p-value	Objective Met
99	96 (97.0%)	1.7%	92.4%	<0.0001	Yes

Note: The p-value was from the exact test.

Hemodynamic Performance

At discharge and throughout 3 years of follow-up, the majority of subjects had no more than mild PR; no subjects presented with severe PR, as shown in Table 16. The average RVOT mean gradient was 16.3 ± 7.1 mmHg at discharge and remained clinically stable throughout follow-up, as shown in Table 17.

Table 16: New Enrollment PAS: Pulmonary Regurgitation by Time Interval – Implanted >24 hours Cohort (N=99)

Degree of Regurgitation[1]	Pre-Implant (n=99)	Discharge (n=99)	6 Months (n=97)	1 Year (n=91)	2 Years (n=49)	3 Years (n=18)
None	2.0% (2/98)	64.6% (62/96)	68.1% (64/94)	63.3% (57/90)	43.8% (21/48)	50.0% (9/18)
Trace	6.1% (6/98)	32.3% (31/96)	25.5% (24/94)	24.4% (22/90)	41.7% (20/48)	33.3% (6/18)
Mild	7.1% (7/98)	3.1% (3/96)	6.4% (6/94)	11.1% (10/90)	8.3% (4/48)	11.1% (2/18)
Moderate	40.8% (40/98)	0.0% (0/96)	0.0% (0/94)	1.1% (1/90)	6.3% (3/48)	5.6% (1/18)
Severe	43.9% (43/98)	0.0% (0/96)	0.0% (0/94)	0.0% (0/90)	0.0% (0/48)	0.0% (0/18)

[1] Table includes data from subjects who have undergone implantation of a subsequent Melody TPV as applicable.

[2] Pulmonary regurgitation was unable to be assessed for 1 subject pre-implant, 3 subjects at discharge, 3 subjects at 6 months, 1 subject at 1 year, and 1 subject at 2 years post-implant.

Table17: New Enrollment PAS: RVOT Mean Gradient by Time Interval – Implanted >24 hours Cohort (N=99)

RVOT Mean Gradient[1]	Pre-Implant (n=99)	Discharge (n=99)	6 Months (n=97)	1 Year (n=91)	2 Years (n=49)	3 Years (n=18)
n	96	92	91	85	44	17
Mean ± SD	33.4±14.1	16.3±7.1	15.0±9.9	15.1±7.1	15.7±8.1	19.5±15.4

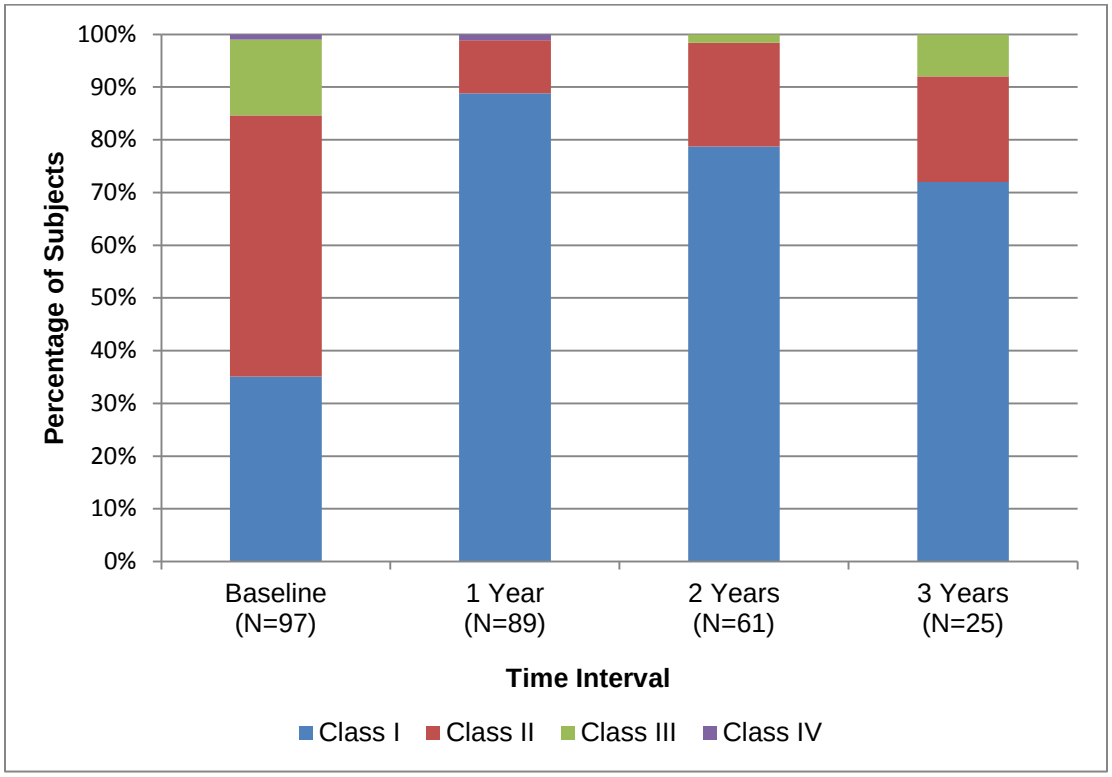
RVOT Mean Gradient[1]	Pre-Implant (n=99)	Discharge (n=99)	6 Months (n=97)	1 Year (n=91)	2 Years (n=49)	3 Years (n=18)
Median [Min, Max]	34.3 [5.6, 70.0]	15.4 [2.5, 40.0]	13.0 [3.0, 83.0]	13.0 [3.0, 34.0]	14.2 [2.8, 38.0]	14.0 [3.0, 55.0]
Q1, Q3	23.5, 43.0	11.0, 20.0	10.0, 18.0	10.0, 20.0	9.6, 20.0	10.0, 22.0

[1] Table includes data from subjects who have undergone implantation of a subsequent Melody TPV as applicable.
[2] RVOT mean gradient was unable to be assessed for 3 subjects pre-implant, 7 subjects at discharge, 6 subjects at 6 months, 6 subjects at 1 year, 5 subjects at 2 years, and 1 subject at 3 years post-implant.

NYHA

Figure 16 presents the NYHA functional class of subjects throughout follow-up. Compared to the Long-term Follow-up PAS, there was a substantially smaller proportion of class II subjects pre-implantation. Following implantation, the majority of subjects were in class I, though the stability is less than what has been observed in the Long-term Follow-up PAS.

Figure 16: New York Heart Association Classification – Implanted >24 hours Cohort (N=99)



X.3. Data Pooling of the Long-term Follow-up PAS and the New Enrollment PAS

A *post hoc* analysis was performed on the pooled data from the Long-term Follow-up PAS and the New Enrollment PAS, with safety and effectiveness outcomes through 1 year of follow-up. The 1-year follow-up duration was selected for this analysis since

all available subjects, in both studies, had surpassed the 1 year visit milestone. TPV dysfunction (defined above) was specified as the primary effectiveness outcome measure.

A. Pooled Subject Demographics

Table 18 presents the demographics and baseline characteristics of the enrolled subjects in the pooled dataset. The baseline demographics were generally similar in the two studies (see Tables 1 and 8 above), with the exceptions that bioprosthetic valve targets and a mixed indication (stenosis and regurgitation) were proportionately more frequent in the New Enrollment PAS.

Table 18: Pooled Subjects Demographics – Enrolled Cohort (N=302)

Assessment	Enrolled Cohort (N=302)
Gender	
Male	64.2% (194/302)
Female	35.8% (108/302)
Age (years)	
n	302
Mean ± SD	21.1 ± 9.8
Median [Min, Max]	18.0 [5.0, 53.0]
Original diagnosis	
Tetralogy of Fallot	44.4% (134/302)
Aortic valve disease (Ross)	18.9% (57/302)
Isolated pulmonary stenosis	2.6% (8/302)
Truncus arteriosus	12.6% (38/302)
Transposition of the great arteries	9.3% (28/302)
Double outlet right ventricle	6.0% (18/302)
Other	6.3% (19/302)
RVOT conduit type	
Homograft	69.5% (210/302)
Biological valved conduit	16.6% (50/302)
Bioprosthesis	8.3% (25/302)
Synthetic	3.3% (10/302)
Other	2.3% (7/302)
RVOT conduit size (mm) when originally implanted	
n	276
Mean ± SD	21.0 ± 3.0
Median [Min, Max]	21.0 [8.0, 30.0]
Bioprosthesis size (mm) when originally implanted	
n	25
Mean ± SD	23.6 ± 3.1
Median [Min, Max]	23.0 [18.0, 31.0]
Primary Indication[1]	
Stenosis	24.2% (71/293)
Regurgitant	51.2% (150/293)
Mixed	24.6% (72/293)
Pulmonary Regurgitation by Site Echo [2]	
None	6.1% (18/293)
Trace	5.1% (15/293)
Mild	10.9% (32/293)

Assessment	Enrolled Cohort (N=302)
Moderate	32.4% (95/293)
Severe	45.4% (133/293)
Mean RVOT Gradient by Site Echo (mmHg)[3]	
n	292
Mean ± SD	32.7 ± 14.4
Median [Min, Max]	33.5 [5.2, 97.0]

[1] Primary Indication was not assessed for 9 New Enrollment PAS subjects that did not meet the hemodynamic inclusion criteria.
[2] Pulmonary regurgitation was unable to be assessed in 3 Long-term Follow-up PAS subjects and 6 New Enrollment PAS subjects.
[3] Mean RVOT gradient was unable to be assessed in 3 Long-term Follow-up PAS subjects and 7 New Enrollment PAS subjects.

B. Pooled Safety Results

Acute Procedure-related Serious Adverse Events

Table 19 provides a summary of the pooled procedure-related adverse events. RVOT conduit rupture or dissection was the most common serious adverse events, occurring in 2.8% of the patients.

Table 19: Summary of Pooled Acute Procedure-related Serious Adverse Events

Procedure-related Serious Adverse Event	Subjects with Event (N=287)
Subjects with procedure-related SAEs	7.3% (21/287)
RVOT conduit rupture or dissection	2.8% (8/287)
Perforation of vessel	1.0% (3/287)
Hemothorax	0.7% (2/287)
Catheter induced arrhythmia	0.7% (2/287)
Other respiratory/pulmonary	0.7% (2/287)
Cardiac arrest	0.3% (1/287)
Coronary compression causing myocardial ischemia	0.3% (1/287)
Fever (at least 39.0°C)	0.3% (1/287)
Hemorrhage: major	0.3% (1/287)
Paravalvular leak: major	0.3% (1/287)
Pseudoaneurysm	0.3% (1/287)
Valve dysfunction: regurgitation	0.3% (1/287)
Ventricular fibrillation	0.3% (1/287)
Vessel dissection	0.3% (1/287)
Other central nervous system	0.3% (1/287)
Other cardiac event	0.3% (1/287)
Other implantation/catheterization	0.3% (1/287)
Other vascular access site complication	0.3% (1/287)

Device-related Adverse Events

Table 20 presents the incidence of device-related adverse events within the first year. Major stent fracture, TPV stenosis, and prosthetic valve endocarditis were the

frequent device-related serious adverse events within the first year of Melody TPV implantation.

Table 20: Summary of Pooled Device-related Adverse Events through1 Year – Implanted Cohort (N=250)

Event	Subjects with Event (N=250)
Subjects with Device-Related SAEs	15.3% (23/250)
Valve dysfunction: stenosis	2.4% (6/250)
Stent fracture: major	2.0% (5/250)
Endocarditis	2.0% (5/250)
Fever (at least 39.0°C)	0.8% (2/250)
Hemothorax	0.8% (2/250)
RVOT conduit rupture or dissection	0.8% (2/250)
Valve dysfunction: regurgitation	0.8% (2/250)
Atrial flutter	0.4% (1/250)
Coronary compression causing myocardial ischemia	0.4% (1/250)
Dizziness	0.4% (1/250)
Hypotension requiring intervention	0.4% (1/250)
Palpitations	0.4% (1/250)
Paravalvular leak: major	0.4% (1/250)
Pneumonia	0.4% (1/250)
Pulmonary thromboembolism	0.4% (1/250)
Sepsis, confirmed (positive blood culture)	0.4% (1/250)
Valve dysfunction: recurrent stenosis	0.4% (1/250)
Ventricular tachycardia	0.4% (1/250)
Other cardiac event	0.4% (1/250)
Other respiratory/pulmonary	0.4% (1/250)

C. Safety and Effectiveness Outcome Measures

Table 21 provides the results of the safety and effectiveness outcome measures utilizing the GEE methodology. Freedom from TPV dysfunction at 1 year is estimated to be 93.3%. Freedom from reoperation, catheter reintervention on the TPV, major stent fracture, and mortality were high.

Table 21: Pooled Rates for Safety and Effectiveness Endpoints Utilizing GEE Methodology

Variable	Analysis Cohort	Number of Subjects in the Analysis	1 year Freedom Rate (95% CI)[3]
TPV dysfunction[1,2]	Implanted >24 hours cohort	243	0.9330 (0.8737, 0.9655)
Reoperation	Implanted >24 hours cohort	248	0.9895 (0.9784, 0.9949)
Re-intervention	Implanted >24 hours cohort	248	0.9845 (0.9508, 0.9952)
Major stent fracture	Implanted >24 hours cohort	248	0.9777 (0.9664, 0.9852)
All-cause mortality	Catheterized cohort	287	0.9957 (0.9906, 0.9981)

[1] The 1 year TPV dysfunction free rate is calculated at day 420 (end of the 1 year window).
[2] TPV dysfunction was unable to be assessed in 5 subjects who did not have an echo performed at or after 1 year; therefore could not be assessed for the composite outcome.
[3] The confidence intervals are calculated without multiplicity adjustment, which are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

X.4. 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 two PAS' included 50 investigators, of which none was full-time or part-time employee of the sponsor and 5 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: 0
- Significant payment of other sorts: 5
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

European and Canadian Post-Market Surveillance Study

The Melody TPV system was granted CE Mark for commercial release in Europe and a Medical Device License from Health Canada for release in Canada in 2006. Following these approvals, the Melody Post-Market Surveillance Study (PMSS) was initiated. It is a prospective, non-randomized, multi-center study being conducted at 7 centers in Europe and Canada. The purpose is to assess the clinical performance of the device over a period of 5 years post implantation.

A total of 71 subjects were enrolled in this study between October 1, 2007 and April 6, 2009. The following data are interim results through March 1, 2014. All 71 subjects underwent catheterization for potential implantation of the Melody TPV; of these, 63 subjects ultimately received the valve. The mean length of follow-up was 50.4 ± 12.6 months.

A. Subject Demographics

Table 22 presents the demographics and baseline data for the enrolled subjects. The study population consisted of 47 male and 24 female subjects with a mean age of 21.6 ± 10.6 (range 8 to 59 years). Tetralogy of Fallot was the most common original diagnosis (46.5%), followed by truncus arteriosus (16.9%).

Table 22: PMSS: Subject Demographics / Baseline Data – Enrolled Cohort (N=71)

Assessment	Enrolled Cohort (N=71)
Gender	
Male	66.2% (47/71)
Female	33.8% (24/71)
Age (years)	
n	71
Mean ± SD	21.6 ± 10.6
Median [Min, Max]	19.0 [8.0, 59.0]
Original diagnosis	
Tetralogy of Fallot	46.5% (33/71)
Aortic valve disease (Ross)	12.7% (9/71)
Isolated pulmonary stenosis	1.4% (1/71)
Truncus arteriosus	16.9% (12/71)
Transposition of the great arteries	14.1% (10/71)
Double outlet right ventricle	4.2% (3/71)
Other[1]	4.2% (3/71)
RVOT conduit type	
Homograft	78.9% (56/71)
Biological valved conduit	4.2% (3/71)
Bioprosthesis	5.6% (4/71)
Bovine	4.2% (3/71)
Other	7.0% (5/71)
RVOT conduit size (mm) when originally implanted	
n	58
Mean ± SD	20.7 ± 3.1
Median [Min, Max]	20.0 [14.0, 29.0]
Bioprosthesis size (mm) when originally implanted	
n	4
Mean ± SD	24.8 ± 2.1
Median [Min, Max]	25.0 [22.0, 27.0]

[1] Other original diagnosis included: double outlet left ventricle (n=1), PA anomaly with pulmonary insufficiency (n=1); and pulmonary atresia with intact ventricular septum (n=1).

B. Procedural Data

A summary of procedural data is provided in Table 23. The percutaneous femoral venous approach was used in the majority of subjects (95.8%); however, in some

patients, internal jugular vein access was used (4.2%). Concomitant procedures were performed in the majority of subjects, most commonly pre-stenting of the RVOT. The mean length of hospital stay was 2.2 ± 1.3 days.

Table 23: PMSS: Procedural Data – Catheterized Cohort (N=71)

Assessment	Catheterized Cohort (N=71)
Venous Site Access	
Femoral vein	95.8% (68/71)
Jugular vein	4.2% (3/71)
Subclavian vein	0.0% (0/71)
Concomitant procedures[1]	
No concomitant procedures	16.9% (12/71)
Stent placement, peripheral PA	4.2% (3/71)
Balloon angioplasty, peripheral PA	0.0% (0/71)
Stent placement, RVOT Conduit	81.7% (58/71)
Placement of intravascular coil	0.0% (0/71)
Closure of ASD or PFO	0.0% (0/71)
Closure of VSD	0.0% (0/71)
Other[2]	5.6% (4/71)
Total fluoroscopy time (minutes)	
n	69
Mean ± SD	32.6 ± 19.1
Median [Min, Max]	30.0 [8.0, 99.9]
Total procedure time (minutes)	
n	68
Mean ± SD	168.2 ± 68.6
Median [Min, Max]	150.5 [68.0, 430.0]
Length of Hospital Stay (days)	
n	67
Mean ± SD	2.2±1.3
Median [Min, Max]	2.0 [1.0, 8.0]

[1] Subjects may have had more than one concomitant procedure performed.
[2] Other concomitant procedures included: balloon dilation of pre-existing conduit stent (n=3), balloon angioplasty of RV-Dacron stenosis (n=1).

C. Safety and Effectiveness Results

Table 24 provides the 1-year, 2-year, and 4-year outcomes data (K-M estimate). Freedom from TPV dysfunction was estimated to be 75.3% at 4 years. Freedoms from reoperation and re-intervention at 4 years were estimated to be 95.0% and 85.0%, respectively. The 4-year freedom from major stent fracture was estimated to be 91.5%, and freedom from all-cause mortality was estimated to be 96.7%.

Table 24: Kaplan-Meier Estimates of the Clinical Outcomes

Variable	Analysis Cohort	1-year K-M Freedom From Rate (95% CI[1])	2-year K-M Freedom From Rate (95% CI)	4-year K-M Freedom From Rate (95% CI)
TPV dysfunction	Implanted >24 hours cohort (N=62)	88.7% (77.6%, 94.5%)	82.1% (69.8%, 89.8%)	75.3% (61.9%, 84.5%)

Variable	Analysis Cohort	1-year K-M Freedom From Rate (95% CI[1])	2-year K-M Freedom From Rate (95% CI)	4-year K-M Freedom From Rate (95% CI)
Reoperation	Implanted >24 hours cohort (N=62)	98.4% (88.9%, 99.8%)	96.7% (87.4%, 99.2%)	95.0% (84.7%, 98.4%)
Re-intervention	Implanted >24 hours cohort (N=62)	91.8% (81.3%, 96.5%)	86.7% (74.9%, 93.2%)	85.0% (72.3%, 92.2%)
Major stent fracture	Implanted >24 hours cohort (N=62)	98.4% (88.8%, 99.8%)	93.4% (83.1%, 97.5%)	91.5% (80.2%, 96.5%)
All-cause mortality	Catheterized cohort (N=71)	98.4% (88.9%, 99.8%)	98.4% (88.6%, 99.8%)	96.7% (86.6%, 99.2%)

[1] The confidence intervals are 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.

XII. 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 Systems Device Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The intended role of the Melody TPV is to restore pulmonary valve function in patients with a dysfunctional RVOT conduit and a clinical indication for pulmonary valve replacement. The Melody TPV is designed to offer a less invasive approach that also extends the longevity of an existing RVOT conduit, deferring (but not necessarily replacing) the need for conduit replacement. The clinical studies demonstrated that the Melody TPV can successfully fulfill this intended role, as demonstrated by the effectiveness outcomes measured in 2 prospective patient cohorts with follow-up extending beyond 5 years. The data indicate that appropriately selected patients can remain free from the need for TPV catheter re-intervention, or RVOT replacement for prolonged periods of time while maintaining favorable hemodynamic parameters.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in clinical studies conducted to support PMA approval as described

above. The results from the nonclinical laboratory and animal studies performed on the Melody TPV and the Ensemble DS demonstrate that this device is suitable for long-term implant. The Melody TPV is intended to be placed with a transcatheter delivery system, and thus does not require cardiopulmonary bypass and open heart surgery typically associated with surgical pulmonary valve replacement. The procedure-related serious adverse events included most commonly RVOT conduit rupture or dissection. However, the clinical studies demonstrated an acceptably low incidence overall of procedure-related complications. The device-related adverse events included most commonly prosthetic valve stent (frame) fracture, prosthetic valve stenosis, and prosthetic valve endocarditis. The clinical studies demonstrated that the overall incidence of morbidity and mortality in follow-up extending beyond 5 years was clinically acceptable. The Melody TPV has been reviewed annually since its HDE approval by the FDA Pediatric Advisory Committee. Although the incidence of some adverse events, particularly endocarditis and RVOT rupture/dissection are notable and merit close observation, the totality of the data supports a reasonable assurance of safety when used according to the Instructions for Use.

C. Benefit-Risk Conclusions

The probable benefits of the Melody TPV include improved pulmonary valve hydrodynamic performance and improved functional status. These improvements can delay the need for surgical replacement of the patient's exiting RVOT conduit. In some patients, delaying surgical conduit re-intervention may reduce the number of open heart surgeries required over the course of their lifetime, thereby decreasing the cumulative morbidity and risk associated with such operations.

The probable risks of the Melody TPV include acute procedure-related serious adverse events (e.g., RVOT conduit rupture/dissection, hemothorax, and vessel perforation) and chronic device-related adverse events (e.g., stent fracture, prosthetic valve stenosis, and prosthetic valve endocarditis).

The data provided above fully support a determination that, for patients with a dysfunctional RVOT conduit and a clinical indication for pulmonary valve replacement, the probable benefits of implanting the Melody TPV outweigh the probable risks.

D. Overall Conclusions

The totality of the clinical data submitted in the PMA application provides reasonable assurance that the Melody TPV system is safe and effective in restoring pulmonary valve competence in patients with a dysfunctional RVOT conduit.

XIV. CDRH DECISION

CDRH issued an approval order on January 27, 2015. The final conditions of approval cited in the approval order are described below.

The applicant must conduct two post-approval studies:

1. *Long-term Follow-up Study*: This study is intended to roll in the long-term (5-year) follow-up study of the IDE cohort specified as a condition of approval for the Melody TPV HDE, H080002, on January 25, 2010.

   The study is a prospective, non-randomized, multi-center, historically controlled clinical trial, designed to follow subjects from the IDE trial up to 5 years. The primary endpoint is freedom from TPV dysfunction, with a performance goal of 36% or greater at 5 years. Secondary endpoints include procedural success, serious procedural- and device-related adverse events, stent fracture, re-intervention on the TPV, surgical replacement of the RVOT conduit, death (all-cause, procedure-related, and device-related), and NYHA classification.

2. *New Enrollment Study*: This study is intended to roll in the new patient enrollment study specified as a condition of approval for the Melody TPV HDE on January 25, 2010.

   The study is a prospective, non-randomized, multi-center, historically controlled clinical trial, designed to assess the postmarket performance of the Melody TPV in a representative population of providers and patients, with 5-year follow-up. The primary endpoint is freedom from TPV dysfunction, with a performance goal of 75% or greater at 6 months. Secondary endpoints include procedural success, serious procedural- and device-related adverse events, stent fracture, re-intervention on the TPV, surgical replacement of the RVOT conduit, death (all-cause, procedure-related, and device-related), and NYHA classification.

In addition, the applicant must provide annual reports of the data from the Melody TPV PB1016 Surveillance Study. The study is a prospective, non-randomized, multi-center, surveillance study, designed to confirm the safety and effective of the new model PB1016 Melody TPV through 2 years of follow-up. The primary endpoint is the percentage of subjects with acceptable hemodynamic function at 6 months post-implant. Secondary endpoints include acceptable hemodynamic function at 1 and 2 years post-implant, procedural success, serious procedural- and device-related adverse events, stent fracture, re-intervention on the TPV, surgical replacement of the RVOT conduit, and death (all-cause, procedure-related, and device-related).

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

XV. 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.