

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; Ensemble™ II Transcatheter Valve Delivery System, models ENS1018, ENS1020, ENS1022
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/S005
Date of FDA Notice of Approval:	February 24, 2017
Priority Review:	Granted priority review status on September 26, 2016 because the availability of the device is in the best interest of the patients.

The original PMA (P140017) was approved on January 27, 2015 and is indicated for use as an adjunct to surgery in the management of pediatric and adult patients with the following 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: \geq moderate regurgitation, and/or
 - Stenosis: mean RVOT gradient \geq 35 mmHg

The SSED to support the indication is available on the CDRH website (http://www.accessdata.fda.gov/cdrh_docs/pdf14/p140017b.pdf) and is incorporated by reference here. The current supplement was submitted to expand the indication for the Melody Transcatheter Pulmonary Valve (TPV) to include the pulmonary valve-in-valve indication, i.e., implantation of a Melody TPV inside a failed pre-existing bioprosthetic pulmonary valve.

II. INDICATIONS FOR USE

The Melody TPV is indicated for use in the management of pediatric and adult patients who have a clinical indication for intervention on a dysfunctional RVOT conduit or bioprosthetic pulmonary valve that has \geq moderate regurgitation and/or a mean RVOT gradient \geq 35 mm Hg.

III. CONTRAINDICATIONS

There are no known contraindications.

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 two (2) components: the Melody TPV and the Ensemble/Ensemble II Delivery System (DS).

Melody 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 two (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 the Melody TPV utilize the same platinum iridium frame, which is expanded at implantation to the respective size.

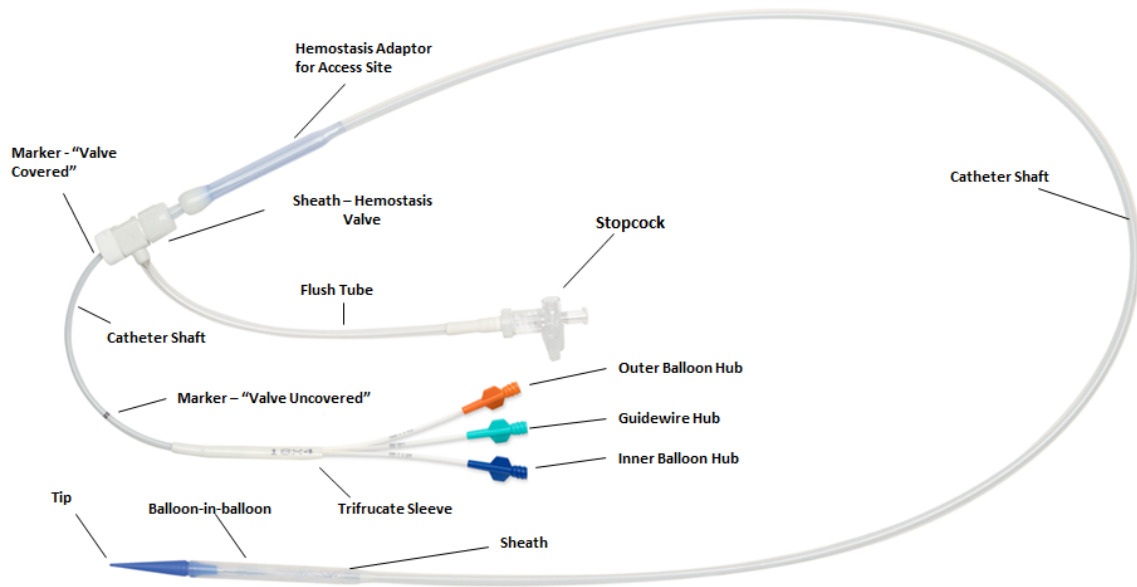
Figure 1: Melody Transcatheter Pulmonary Valve



Ensemble DS

The Ensemble DS is designed to deliver a mounted Melody TPV via venous access to a failing RVOT conduit or pulmonary bioprosthesis 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.

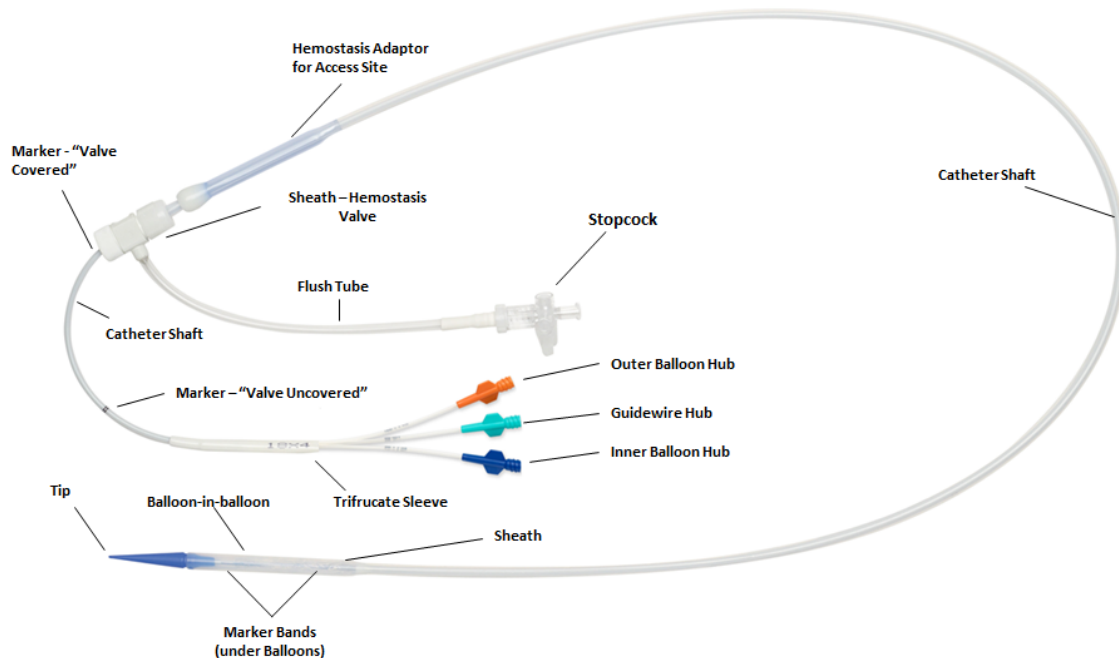
Figure 2: Ensemble Delivery System



Ensemble II DS

The Ensemble II DS is a design iteration of the Ensemble DS, with the addition of radiopaque marker bands to aid in visibility of balloon location under fluoroscopy and some material changes. It also comes in outer balloon sizes of 18, 20, and 22 mm (ENS1018, ENS1020, and ENS1022, respectively).

Figure 3: Ensemble II Delivery System



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are two (2) alternatives for the correction of dysfunctional bioprosthetic valves in the pulmonary position: balloon valvuloplasty and surgical replacement of the bioprosthetic valve with a homograft, valved conduit, or another 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 has not been marketed in the United States or any foreign country for the indication of replacing a dysfunctional bioprosthetic valve in the pulmonary position.

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 device:

Potential procedural complications:

- 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 post-implantation complications:

- Stent fracture¹
- Stent fracture resulting in recurrent obstruction
- Endocarditis
- Embolization or migration of the TPV
- Valvular dysfunction (stenosis or regurgitation)

¹The 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.

- 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 by accessing the SSED for the original PMA.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant collected clinical data to establish a reasonable assurance of safety and effectiveness of the Melody TPV for implanting into a dysfunctional bioprosthetic valve in the pulmonary position. The clinical data supporting the PMA supplemental approval decision were pooled from the following three (3) sources:

- Melody TPV Long-term Follow-up Post Approval Study (PAS): 8 patients
- Melody TPV New Enrollment PAS: 17 patients
- Real-World Data: 100 patients

A. Study Designs

Melody TPV Long-term Follow-up PAS:

The Melody TPV Long-term Follow-up PAS is a prospective, non-randomized, multi-center clinical study. The patients in this study were originally enrolled under IDE G050186 and were continued to be followed under a PAS first under HDE H080002 and then under PMA P140017 after the HDE was converted to a PMA. Eight (8) patients who received a Melody TPV within their dysfunctional pulmonary bioprosthesis were included in this study. These patients were a subset of the patients enrolled in the PAS, with the rest being patients who received a Melody TPV inside their dysfunctional RVOT conduit, which was the indication approved under HDE H080002 and PMA P140017. The eight (8) patients were enrolled at five (5) centers in the United States between June 14, 2007, and November 30, 2009. The mean length of follow-up was 78.8 ± 12.7 months with a cumulative follow-up of 52.5 patient-years.

Further information on the study design of this PAS can be found in the SSED for the original PMA.

Melody TPV New Enrollment PAS:

The Melody TPV New Enrollment PAS is a prospective, non-randomized, multi-center clinical study. The patients in this study were originally enrolled under a PAS under HDE

H080002 and then were continued to be followed under PMA P140017. Seventeen (17) patients who received a Melody TPV within their dysfunctional pulmonary bioprosthesis were included in this study. These patients were again a subset of the patients enrolled in the PAS; the remaining patients received a Melody TPV inside their dysfunctional RVOT conduits. The 17 patients were enrolled at seven (7) centers in the United States between November 5, 2010, and July 12, 2012. The mean length of follow-up was 44.3 ± 14.2 months with a cumulative follow-up of 62.8 patient-years.

Further information on the study design of this PAS can again be found in the SSED for the original PMA.

Real-World Data:

The real-world data were collected via a retrospective, non-randomized, multi-center clinical study. Given the limitations of a retrospective study and expected missing data, the study enrolled a total of 100 consecutive patients who were implanted with a Melody TPV within a dysfunctional bioprosthetic valve in the pulmonary position between January 25, 2010 (HDE approval), and June 1, 2015, at 10 centers in the United States, with a goal to reach about 50 patients having complete 1-year data. The mean length of follow-up was 16.6 ± 15.3 months with a cumulative follow-up of 138.6 patient-years.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the retrospective study was limited to patients who met the following inclusion criterion:

- Previous implantation of a Melody TPV within a failed stented bioprosthesis in the pulmonary position with a rigid circumferential sewing ring in the RVOT that was expanded to no greater than 22 mm at the time of implantation

Patients were excluded from the retrospective study if they met any of the following exclusion criteria:

- Previous or current participation in a Medtronic-sponsored Melody TPV study
- Implantation of the Melody TPV within a dysfunctional bioprosthetic valve in the aortic, mitral, or tricuspid position

2. Follow-up Schedule

Clinical data were collected retrospectively at baseline, implant procedure, discharge, 6 months, and annually through most recent follow-up during the study period. Data collected included demographics and medical history, procedural information, adverse event assessments, transthoracic echocardiogram (when available), and radiography (fluoroscopy and/or x-ray when available).

3. Clinical Endpoints

The primary objective of this study was to evaluate safety and effectiveness of the Melody TPV used within a dysfunctional bioprosthetic valve in the pulmonary position at 1 year. The following clinical endpoints were identified:

Safety:

- Procedure-related serious adverse events
- Device-related serious adverse events
- All-cause mortality

Effectiveness:

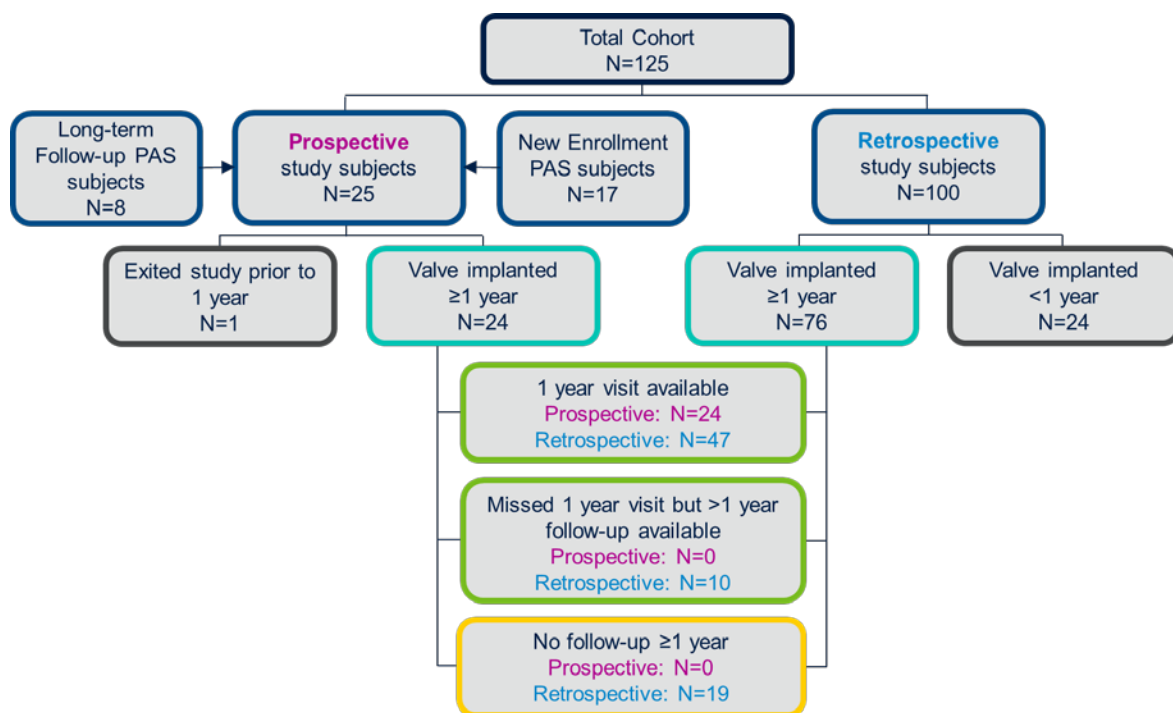
- Procedural success
- TPV dysfunction, defined as follows:
 - Reoperation device-related reasons,
 - Catheter re-intervention on the TPV,
 - Hemodynamic dysfunction of the TPV (\geq moderate pulmonary regurgitation and/or a mean RVOT gradient > 40 mmHg)
- Reoperation on the TPV
- Catheter re-intervention on the TPV
- Hemodynamic performance

The three (3) data sets listed above were pooled and analyzed descriptively. The success criterion was based on clinical judgement.

B. Accountability of Study Subjects

At the time of database lock, of 125 patients pooled from the three (3) studies outlined above, 56.8% (71) patients were available for analysis at the completion of the study, the 1-year post-implant visit. The detailed patient accountability is shown in Figure 4.

Figure: 4 Patient Accountability Chart



C. Study Population Demographics and Baseline Characteristics

The demographics of the study population are typical for a transcatheter pulmonary valve study performed in the US. The pooled subject demographics and baseline characteristics are summarized in Table 1.

Table 1: Subject Demographics and Baseline Characteristics

Assessment	Result (N=125)
Weight (kg)	
n	124
Mean ± SD	63.2 ± 24.5
Median [Min, Max]	60.6 [15.0, 161.2]
Q1, Q3	46.7, 78.8
Gender	
Female	45.6% (57/125)
Male	54.4% (68/125)
Age at time of baseline (years)	
n	125
Mean ± SD	24.5 ± 12.3

Assessment	Result (N=125)
Median [Min, Max]	22.0 [5.0, 79.0]
Q1, Q3	15.0, 31.0
Original Diagnosis¹	
Aortic valve disease (Ross)	1.6% (2/125)
Double outlet right ventricle	4.0% (5/125)
Isolated pulmonary stenosis	10.4% (13/125)
Pulmonary Atresia	5.6% (7/125)
With intact ventricular septum	4.0% (5/125)
With ventricular septal defect	1.6% (2/125)
Tetralogy of Fallot	72.8% (91/125)
With pulmonary stenosis	56.8% (71/125)
With pulmonary atresia	9.6% (12/125)
Absent pulmonary valve	4.8% (6/125)
Transposition of the great arteries	2.4% (3/125)
Truncus arteriosus	2.4% (3/125)
Other diagnosis ²	8.8% (11/125)
Bioprosthesis Size per Label (mm)	
18	0.8% (1/122)
19	7.4% (9/122)
20	0.8% (1/122)
21	15.6% (19/122)
23	27.9% (34/122)
25	27.0% (33/122)
27	10.7% (13/122)
29	7.4% (9/122)
31	1.6% (2/122)
33	0.8% (1/122)
Primary Indication	
Stenosis	16.4% (20/122)
Regurgitant	35.2% (43/122)
Mixed	48.4% (59/122)
Number of Previous Open Heart Surgeries	
n	123

Assessment	Result (N=125)
Mean ± SD	2.3 ± 0.9
Median [Min, Max]	2.0 [1.0, 8.0]
Q1, Q3	2.0, 3.0
Pulmonary Regurgitation by Site Echo	
None	0.0% (0/119)
Trace	5.0% (6/119)
Mild	9.2% (11/119)
Moderate	37.8% (45/119)
Severe	47.9% (57/119)
Bioprosthesis Mean Gradient by Site Echo (mmHg)	
n	103
Mean ± SD	29.5 ± 12.6
Median [Min, Max]	29.0 [3.5, 69.0]
Q1, Q3	21.7, 37.0
Number of Previous Bioprosthetic Valves	
0	15.3% (19/124)
1	66.1% (82/124)
2	13.7% (17/124)
3	4.0% (5/124)
4	0.8% (1/124)
¹ Subjects may have had more than one original diagnosis	
² Other original diagnosis included: right sided carcinoid valvular heart disease (n=1); Cornelia DeLang (n=1); pulmonary valve endocarditis (n=1); hypoplastic pulmonary arteries (n=1); branch PA stenosis (n=1); secundum atrial septal defect (ASD) (n=1); ventricular septal defect (VSD) (n=1); right aortic arch (n=1); multiple aortopulmonary (n=1); partially anomalous pulmonary venous connection (n=1); and chronic biventricular heart with pulmonary hypertension, atrial flutter; diabetes mellitus, and chronic lung disease; at the time of procedure he was being maintained on Milrinone infusion (n=1).	

D. Safety and Effectiveness Results

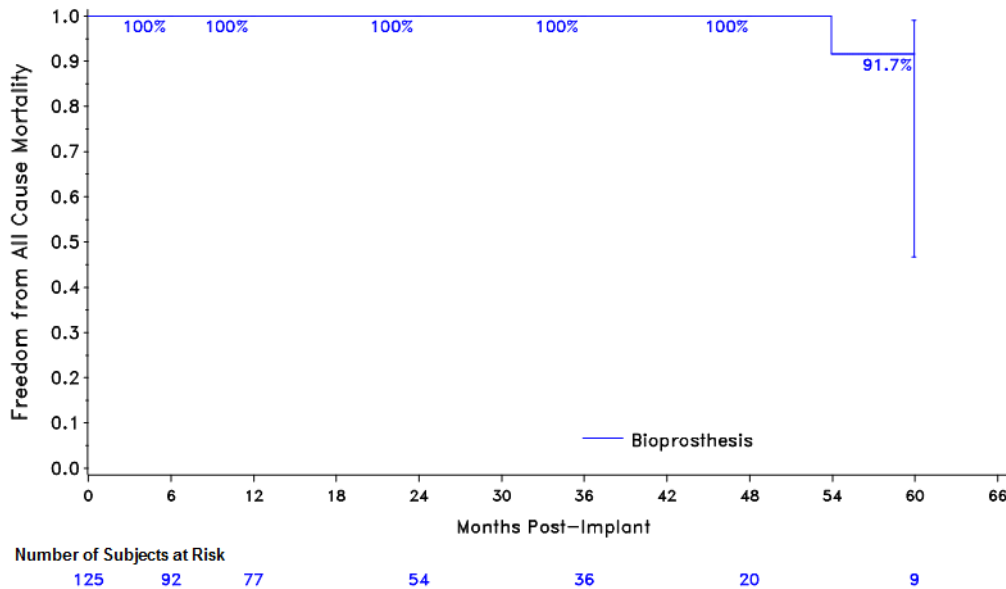
Although the pre-specified time point for the pooled analysis was at one year, all available safety and effectiveness results over a 5-year follow-up period are summarized below, unless otherwise specified. Note that data beyond one year are scant due to missing data and/or implant duration.

1. Safety Results

Freedom from All-cause Mortality

The Kaplan-Meier (K-M) rates for freedom from all-cause mortality through 5 years are shown in Figure 5. There was no mortality for any cause at one year among available patients.

Figure 5: K-M Curve - Freedom from All-cause Mortality



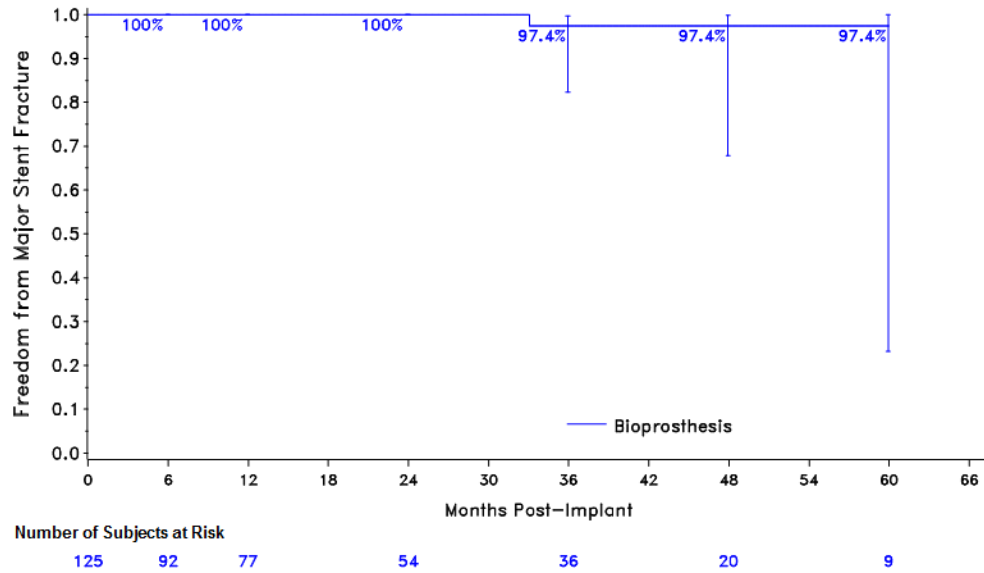
Notes:

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

Freedom from Major Stent Fracture

The K-M rates of freedom from major stent fracture through 5 years are shown in Figure 6. There was no major stent fracture at one year among available patients.

Figure 6: K-M Curve - Freedom from Major Stent Fracture



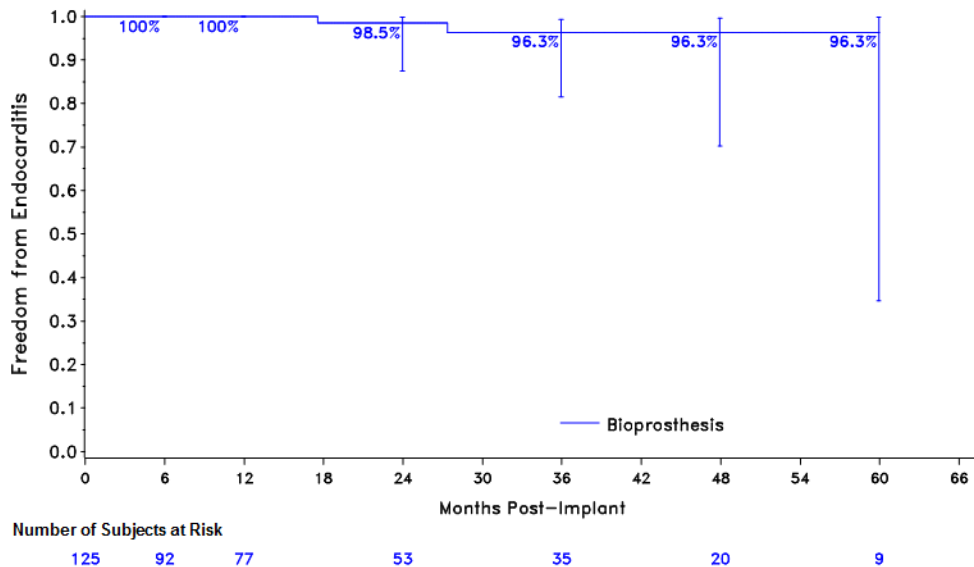
Notes:

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

Freedom from Endocarditis

The K-M rates of freedom from endocarditis through 5 years are shown in Figure 7. There was no endocarditis at one year among available patients.

Figure 7: K-M Curve - Freedom from Endocarditis



Notes:

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

Acute Procedure-related Serious Adverse Events

The procedure-related serious adverse events identified in the first year are summarized in Table 2.

Table 2: Summary of Procedure-Related Serious Adverse Events in the First Year

Procedure-Related Serious Adverse Event	Result (N=125)
Subjects with Procedure-Related SAEs	4.0% (5/125)
Cardiac arrest	0.0% (0/125)
Catheter induced arrhythmia	0.8% (1/125)
Congestive heart failure	0.8% (1/125)
Coronary compression causing myocardial ischemia	0.0% (0/125)
Dizziness	0.0% (0/125)
Endocarditis	0.0% (0/125)
Fever (at least 39.0°C)	0.0% (0/125)

Procedure-Related Serious Adverse Event	Result (N=125)
Hemorrhage: major	0.8% (1/125)
Hemorrhage: minor	0.0% (0/125)
Hemothorax	0.0% (0/125)
Hypotension requiring intervention	0.0% (0/125)
Paravalvular leak: major	0.0% (0/125)
Perforation of vessel	0.0% (0/125)
Pseudoaneurysm	0.8% (1/125)
Pulmonary thromboembolism	0.0% (0/125)
Sepsis, confirmed (positive blood culture)	0.0% (0/125)
Stent fracture: major	0.0% (0/125)
Valve dysfunction: regurgitation	0.0% (0/125)
Venous thrombosis, definite	0.8% (1/125)
Ventricular fibrillation	0.0% (0/125)
Ventricular tachycardia	0.0% (0/125)
Vessel dissection	0.0% (0/125)
Other cardiac event	0.0% (0/125)
Other central nervous system	0.0% (0/125)
Other respiratory/pulmonary	0.0% (0/125)
Other vascular access site complication	1.6% (2/125)
Total Number of Events	7

Device-related Serious Adverse Events

The device-related serious adverse events identified in the first year are summarized in Table 3.

Table 3: Summary of Device-Related Serious Adverse Events in the First Year

Device-Related Serious Adverse Event	Result (N=125)
Subjects with Device-Related SAEs	2.4% (3/125)
Atrial flutter	0.0% (0/125)
Coronary compression causing myocardial ischemia	0.0% (0/125)
Dizziness	0.0% (0/125)
Endocarditis	0.0% (0/125)
Fever (at least 39.0°C)	0.0% (0/125)
Hemothorax	0.0% (0/125)
Hypotension requiring intervention	0.0% (0/125)
Palpitations	0.0% (0/125)
Paravalvular leak: major	0.0% (0/125)

Device-Related Serious Adverse Event	Result (N=125)
Pneumonia	0.0% (0/125)
Pulmonary thromboembolism	0.0% (0/125)
Sepsis, confirmed (positive blood culture)	0.0% (0/125)
Stent fracture: major	0.0% (0/125)
Valve dysfunction: recurrent stenosis	0.0% (0/125)
Valve dysfunction: regurgitation	0.8% (1/125)
Valve dysfunction: residual stenosis	1.6% (2/125)
Valve dysfunction: stenosis	0.0% (0/125)
Ventricular tachycardia	0.0% (0/125)
Other cardiac event	0.0% (0/125)
Total Number of Events	3

2. Effectiveness Results

Procedural Success

Acute procedural success was defined as the percentage of subjects with a Melody™ TPV implant attempted with the TPV fixated within the desired location, an RV-PA peak-to-peak gradient <35 mm Hg measured in the catheterization lab postimplant, less than mild pulmonary regurgitation by angiography postimplant, and free of explant at 24 hours postimplant. The procedural success rate is presented in Table 4.

Table 4: Procedural Success

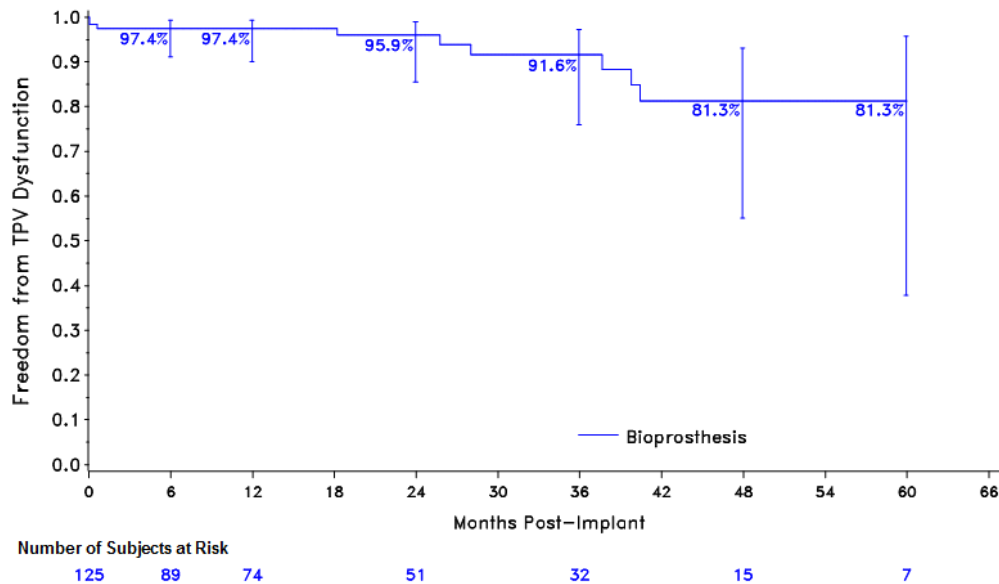
Procedural Outcome	Result (N=125)
Procedural Success ¹	88.9% (104/117)
Procedural Failure	11.1% (13/117)
Melody TPV not fixated within the desired location	0.0% (0/125)
RV-PA peak-to-peak gradient (measured in the catheterization lab) at least 35 mmHg post-implant	0.8% (1/123)
More than trivial pulmonary regurgitation by angiography post-implant	10.1% (12/119)
Explant of the Melody TPV within 24 hours post-implant	0.0% (0/125)

¹One or more elements of procedural success were not able to be determined for eight (8) subjects.

Freedom from TPV Dysfunction

The K-M rates of freedom from TPV dysfunction (as defined above) through 5 years are shown in Figure 8. The rate was 97.4% at one year among available patients.

**Figure 8: K-M Freedom from TPV Dysfunction – Implanted >24 hours Cohort (N=125)
– Approach 1**



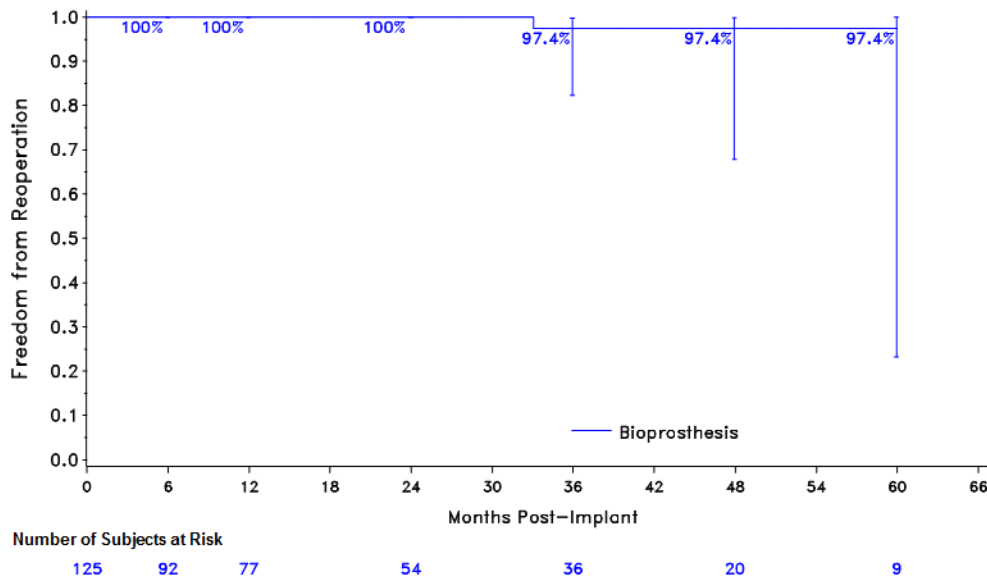
Notes:

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

Freedom from Reoperation on the TPV

The K-M rates of freedom from reoperation on the TPV through 5 years are shown in Figure 9. There was no reoperation on the TPV at one year among available patients.

Figure 9: K-M Curve - Freedom from RVOT Reoperation – Implanted <24 hours Cohort (N=125)



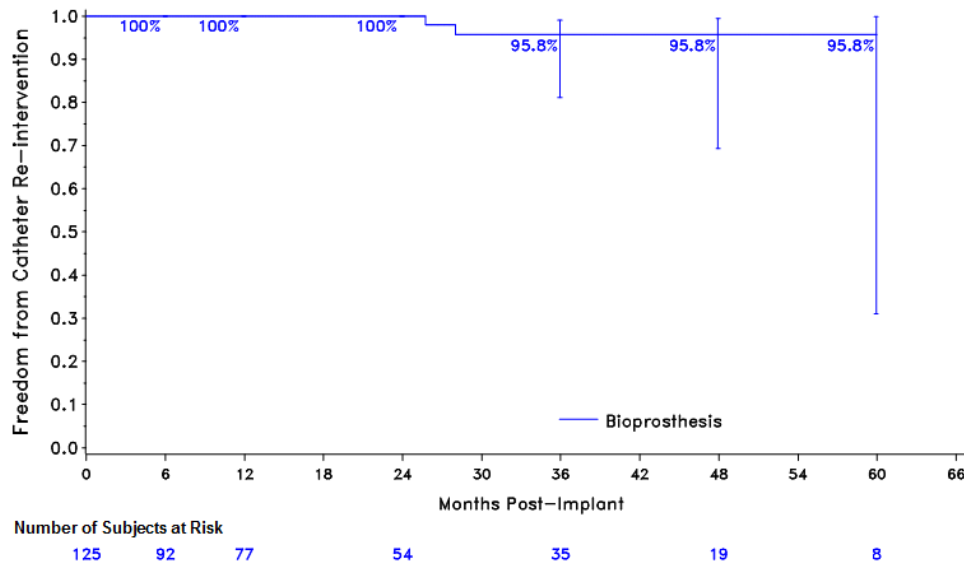
Notes:

1. 0 = 0 to 182 days, 6 = 183 to 364 days, 12 = 365 to 729 days, 24 = 730 to 1094 days, 36 = 1095 to 1459 days, 48 = 1460 to 1824 days, and 60 = 1825 to 2189 days.
2. The cumulative probability of event free estimate is based on the K-M method.
3. The confidence interval (CI) is the log-log transformed 95% CI using the Peto standard error. The CIs are calculated without multiplicity adjustment. The adjusted CIs could be wider than presented here. As such, CIs 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

The K-M rates of freedom from catheter re-intervention on the TPV through 5 years are shown in Figure 10. There was no catheter re-intervention on the TPV at one year among available patients.

Figure 10: K-M Freedom from Catheter Re-intervention on the TPV – Implanted >24 hours Cohort (N=125)



Notes:

1. 0 = 0 to 182 days, 6 = 183 to 364 days, 12 = 365 to 729 days, 24 = 730 to 1094 days, 36 = 1095 to 1459 days, 48 = 1460 to 1824 days, and 60 = 1825 to 2189 days.
2. The cumulative probability of event free estimate is based on the K-M method.
3. The confidence interval (CI) is the log-log transformed 95% CI using the Peto standard error. The CIs are calculated without multiplicity adjustment. The adjusted CIs could be wider than presented here. As such, CIs are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Hemodynamic Performance

The distribution of degree of pulmonary regurgitation and average mean RVOT gradient are shown in Figures 11 and 12, respectively.

Figure 11: Pulmonary Regurgitation

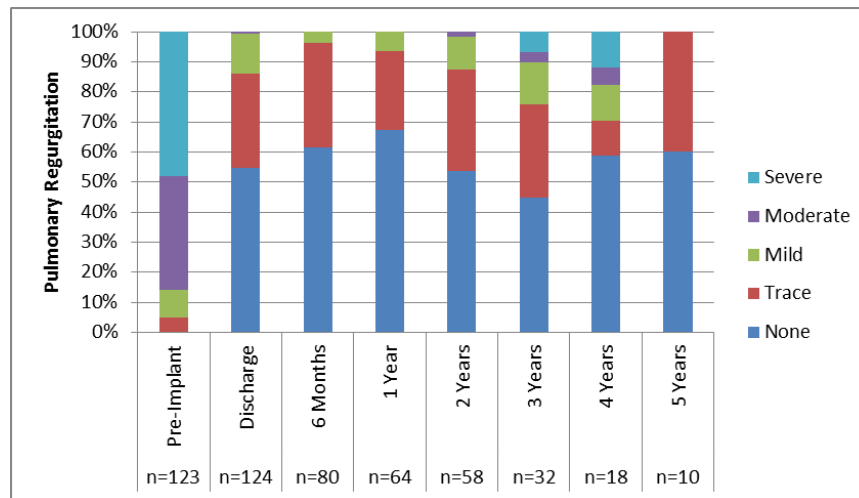
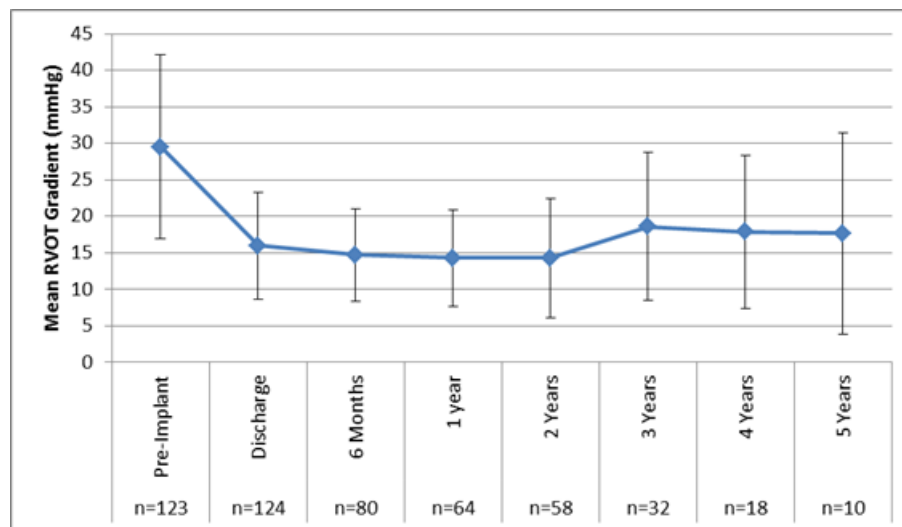


Figure 12: Mean RVOT Gradient



3. Procedural Data

A summary of the procedural data is provided in Table 5.

Table 5: Procedural Data

Variable	Result (N=125)
Venous Site Access	
Femoral vein	95.2% (119/125)
Internal jugular vein	4.8% (6/125)
Other	0.0% (0/125)
Size of Delivery System	
18 mm	3.3% (4/123)
20 mm	15.4% (19/123)
22 mm	81.3% (100/123)
Concomitant Procedures¹	
No concomitant procedures	68.8% (86/125)
Stent placement, peripheral PA	7.2% (9/125)
Balloon angioplasty, peripheral PA	4.8% (6/125)
Stent placement, Bioprosthetic Valve	15.2% (19/125)
Placement of intravascular coil	0.0% (0/125)
Closure of ASD or PFO	1.6% (2/125)
Closure of VSD	0.0% (0/125)
Other ²	7.2% (9/125)
Length of Hospital Stay (days)	
n	125
Mean ± SD	1.2 ± 0.8
Median [Min, Max]	1.0 [0.0, 7.0]
Q1, Q3	1.0, 1.0
Narrowest Dimension at Intended Site of Implantation (mm)	
n	100
Mean ± SD	17.1 ± 3.2
Median [Min, Max]	17.0 [8.0, 24.0]
Q1, Q3	15.0, 19.7
Sizing Balloon Waist (after Pre-dilation if Performed (mm))	
n	90
Mean ± SD	17.9 ± 3.9
Median [Min, Max]	18.9 [0.0, 23.1]
Q1, Q3	16.9, 20.0
Melody TPV Implanted in the Desired Location	

Variable	Result (N=125)
Yes	100.0% (125/125)
No	0.0% (0/125)
Explant	
Free of explant of the Melody TPV 24 hours post-implant	100.0% (125/125)

¹Subjects may have had more than one concomitant procedure.

²Other concomitant procedures included: pulmonary valvuloplasty (n=4); existing pulmonary artery (PA) stent re-dilation (n=3); vascular plugs placed in main PA and right iliac vein stented (n=1); and Melody TPV implanted in tricuspid position (n=1).

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population. This submission included pediatric data 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 three (3) studies included 73 unique investigators, of which none was a full-time or part-time employee of the sponsor and six (6) 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: 2
- 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. 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)(3) 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.

XII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The Melody TPV provides an alternative to surgical replacement of dysfunctional bioprosthetic valves in the pulmonary position by providing a competent valve in a less invasive manner. The effectiveness of the procedure is supported by improved hemodynamic performance and freedom from surgical or catheter intervention post implantation. The mean RVOT gradient was reduced from 29.5 ± 12.6 mmHg at baseline to 14.3 ± 6.6 mmHg at one year post-implantation, and the degree of pulmonary regurgitation was markedly reduced with all patients having no more than mild pulmonary regurgitation at one year versus 14.2% at baseline. In addition, there was no reoperation or catheter re-intervention on the TPV at one year among available patients.

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. In the first year, the procedure- and device-related serious adverse events were reported in 4.0% and 2.4% of the patients, respectively. The most common procedure- and device-related serious adverse events were vascular access site complications and residual stenosis. However, the rates of these two (2) events were relatively low (1.6% for both). Some other risks associated with implantation of the Melody TPV inside an RVOT conduit (refer to P140017 SSED), such as conduit rupture, coronary compression, and stent fracture, seemed to be less prevalent with the Melody pulmonary valve-in-valve patients. Although no endocarditis was reported at one year among all available patients, literature has reported various rates of endocarditis in Melody TPV patients, which merits close observation. Given the totality of available clinical data, the Melody TPV has demonstrated a reasonable assurance of safety for pulmonary valve-in-valve implantation.

C. Benefit-Risk Determination

The probable benefits of the Melody TPV for pulmonary valve-in-valve implantation are based on data collected to support PMA approval as described above. The probable benefits include improved pulmonary valve hemodynamic performance and delayed need for surgical replacement of the patient's existing dysfunctional surgical bioprosthesis. In some patients, delaying surgical 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., vascular access site complication, catheter induced arrhythmia, and major bleeding) and chronic device-related adverse events (e.g., prosthetic valve dysfunction and prosthetic valve endocarditis).

One additional factor considered in determining probable benefits and risks of the Melody TPV device in treating patients with a dysfunctional surgical bioprosthetic pulmonary valve was the limitations of the real-world data (i.e., the third study outline above), specifically missing data in real-world clinical practice settings. Despite this limitation, the real-world evidence was found to be consistent with the evidence collected in prospective trial settings (i.e., the Long-term Follow-up PAS and the New Enrollment PAS) and also consistent with the evidence seen in patients with a dysfunctional RVOT conduit (refer to P140017 SSED).

1. Patient Perspectives

This submission did not include specific information on patient perspectives for this device. However, since the pulmonary valve-in-valve procedure using the Melody TPV provides a less invasive alternative to surgical re-intervention, FDA believes many patients would prefer the transcatheter approach.

In conclusion, the available clinical data summarized above support a determination that for patients with a dysfunctional surgical bioprosthesis and a clinical indication for pulmonary valve replacement, the probable benefits of implanting the Melody TPV outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the Melody TPV when used in accordance with the indications for use. Transcatheter implantation of a Melody TPV within a dysfunctional surgical pulmonary bioprosthesis offers the benefit of delaying or even avoiding surgical re-intervention needed to restore the hemodynamic competence of the pulmonary valve, thus reducing the number of open heart surgeries required over the course of a patient's lifetime. The benefit of the therapy outweighs the risks associated with it.

XIII. CDRH DECISION

CDRH issued an approval order on February 24, 2017.

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.