Melody™

Transcatheter Pulmonary Valve

Ensemble™

Transcatheter Valve Delivery System

Instructions for Use

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician.

Explanation of symbols on package labeling

	Model
	Use By
	Consult Instructions for Use at this Website
	Do Not Reuse
	Size
	Serial Number
	Sterile LC: Device has been sterilized using Liquid Chemical Sterilants according to EN/ISO 14160.
	Catalog Number
	Temperature Limit
	Quantity
	Lot Number
	Sterilized Using Ethylene Oxide
	Open Here
	Nonpyrogenic
	MR Conditional
	Maximum Guidewire Compatibility
	Rated Burst Pressure
	Do Not Exceed Rated Burst Pressure
	Do Not Resterilize
	Manufacturer
	Do Not Use if Indicator Turns Black
	Do Not Use if Package is Damaged
	Keep Away from Sunlight

! USA For US Audiences Only

1.0 Device Description

The implant system consists of 2 components: the Melody™ transcatheter pulmonary valve, model PB10 (stented bovine jugular vein valve) and the Ensemble™ transcatheter valve delivery system, model NU10. The Melody™ transcatheter pulmonary valve (TPV) consists of a heterologous (bovine) jugular vein valve sutured within a laser-welded, platinum-iridium stent with gold brazing of the welds. The Melody™ TPV is available in 2 sizes: a 16 mm bovine jugular vein (nominal length of 30 mm) that can be expanded to ≤20 mm and an 18 mm bovine jugular vein (nominal length of 28 mm) that can be expanded to ≤22 mm. A final sterilization step is performed using a sterilant that contains 1% glutaraldehyde and 20% isopropyl alcohol, and in which the valve is preserved and packaged until used. Adequate rinsing with isotonic saline solution must be performed before implantation to reduce the glutaraldehyde concentration.

The Ensemble™ transcatheter valve delivery system consists of a balloon-in-balloon catheter with a retractable polytetrafluoroethylene (PTFE) sheath large enough to cover the valve after crimping. The delivery system has a 22-Fr crossing profile. At inflation, the inner balloon is half the diameter of the outer balloon. Both balloons are made of nylon. The delivery system comes in outer balloon sizes of 18, 20, and 22 mm. The catheter's sheath has a side-port used to flush the system and a hemostatic sleeve over the sheath to minimize bleeding at the insertion site. The catheter has a polyether block amide (PEBAX®, Arkema Corporation) distal obturator that is conical in shape. The delivery system is compatible with a 0.889-mm (0.035-in) guidewire.

2.0 Indications for Use

The Melody™ TPV is intended 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) 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 mm Hg

3.0 Contraindications

There are no known contraindications for the Melody™ TPV.

4.0 Warnings and Precautions

4.1 Warnings

DO NOT implant in the aortic or mitral position. Preclinical bench testing of the Melody™ TPV suggests that valve function and durability will be extremely limited when used in these locations.

DO NOT use if patient's anatomy precludes introduction of the valve, if the venous anatomy cannot accommodate a 22-Fr size introducer, or if there is significant obstruction of the central veins.

DO NOT use if there are clinical or biological signs of infection including active endocarditis. Standard medical and surgical care should be strongly considered in these circumstances.

Procedural

The potential for compression of a coronary artery should be considered in all patients undergoing TPV implantation. Assessment of the coronary artery anatomy for the risk of compression should be performed in all patients prior to deployment of the TPV. Aortography should be performed to define the anatomy of the coronary arteries and their relationship to the conduit. If aortography demonstrates a coronary artery branch passing beneath or otherwise close to the conduit, or if coronary anatomy could not be determined, further evaluation with selective coronary arteriography and simultaneous inflation of an angioplasty balloon across the conduit obstruction should be performed. If inflation of the balloon demonstrates any suggestion of coronary compression, as demonstrated by simultaneous selective coronary arteriography, the conduit should be deemed anatomically unsuitable for TPV implantation.

The risk of conduit rupture should be considered in all patients undergoing TPV implantation. To minimize the risk of conduit rupture, do not use a balloon with a diameter greater than 110% of the nominal diameter (original implant size) of the conduit for predilation of the intended deployment site or for deployment of the TPV.

TPV

The RVOT is a dynamic structure, and stents placed in the RVOT may be exposed to complex cyclic stresses related to the cardiac cycle. The risk factors for stent fracture after TPV implant have not been fully defined. However, prominent mechanical stresses on the outflow tract stent, such as compression between the anterior chest wall and heart, appear to be associated with an increased risk of stent fracture. Other factors are likely to contribute to the risk of stent fracture as well.

The potential for stent fracture should be considered in all patients who undergo TPV placement, regardless of the previously discussed or subsequently characterized risk factors. Radiographic assessment of the stent with chest radiography or fluoroscopy should be included in the routine postprocedural evaluation of patients who receive a TPV. In particular, in patients found to have a substantial increase in the degree of RVOT obstruction, the possibility of an associated stent fracture should be considered and evaluated. If a stent

fracture is detected, continue monitoring the valve performance in conjunction with clinically appropriate hemodynamic assessment. In patients with stent fracture and significant associated RVOT obstruction or regurgitation, reintervention should be considered in accordance with usual clinical practice (Section 6.2).

Limited data are available on the clinical performance of reimplantation of another Melody™ TPV within the original Melody™ TPV.

This device was designed for single patient use only. Do not reuse, reprocess, or resterilize this product. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device and/or create a risk of contamination of the device, which could result in patient injury, illness, or death.

DO NOT RESTERILIZE THE VALVE BY ANY METHOD. Exposure of the device and container to irradiation, steam, ethylene oxide, or other chemical sterilants will render the device unfit for use.

DO NOT use the device if:

- the device has been dropped, damaged, or mishandled in any way
- the Use By date has elapsed
- each tamper-evident seal is broken
- the serial number tag on the valve does not match the serial number on the container label
- the shipping temperature indicator window inside the shelf carton is black. If the shipping temperature indicator is black, the valve is not suitable for clinical use.
- the storage solution does not completely cover the device or there is evidence of leakage

DO NOT expose the device to solutions other than the storage and rinsing solutions.

DO NOT add antibiotics to either the storage or the rinse solution. Do not apply antibiotics to the device.

DO NOT allow the device to dry. Maintain tissue moisture with irrigation or immersion.

DO NOT attempt to repair a damaged device.

DO NOT handle or use forceps to manipulate the valve leaflet tissue.

DO NOT use forceps to manipulate the stent.

DO NOT overexpand the device beyond the maximum recommended size, which is 20 mm for Melody™ TPV catalog number PB1016 and 22 mm for Melody™ TPV catalog number PB1018, as this may result in a regurgitant TPV.

Delivery System

This device was designed for single patient use only. Do not reuse, reprocess, or resterilize this product. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device and/or create a risk of contamination of the device, which could result in patient injury, illness, or death.

DO NOT use air or any gaseous substance as a balloon-inflation medium.

DO NOT advance the guidewire, balloon-dilatation catheter, or any other component if resistance is met, without first determining the cause and taking remedial action.

DO NOT remove the guidewire from the catheter at any time during the procedure.

Other

Safety and effectiveness of the device has not been demonstrated in pregnant patients.

Because of the inherent risks cited above, institutions planning to implant the Melody™ TPV should be prepared to urgently proceed to surgical intervention with cardiopulmonary bypass or with urgent implementation of extracorporeal membrane oxygenation (ECMO) support.

4.2 Precautions

- Rinsing procedures of the TPV must be strictly followed.
- Exposure to glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure to or breathing of the chemical vapor. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water for a minimum of 15 minutes. In the event of eye contact, flush with water for a minimum of 15 minutes and seek medical attention immediately.
- The sealed catheter packaging should be inspected prior to opening. If the seal is broken or the packaging has been damaged, sterility cannot be assured.
- Proper functioning of the catheter depends on its integrity. Use caution when handling the catheter. Damage may result from kinking, stretching, or forceful wiping of the catheter.
- This catheter is not recommended for pressure measurement or delivery of fluids.
- Maintain tight catheter connections and use aspiration before proceeding to avoid air introduction into the system.
- The delivery system must be carefully flushed to avoid the introduction of air bubbles.
- Before crimping (reducing) the size of the valve on the balloon, the orientation should be verified.

  Note: The blue suture should be adjacent to the blue tip of the catheter.
- Do not remove the tag attached to the valve until the valve is ready to be crimped onto the delivery system, and implantation is imminent. This tag, along with the blue suture, identifies the outflow end of the valve and helps with proper orientation of the TPV on the delivery system.
- The inflation diameter of the balloon used during valve delivery should approximate the diameter of the obstructive vessel and the intended implant site.
- The crimping procedure must be carried out carefully. While crimping, the orientation of the TPV must be known at all times. No change of orientation should occur as the valve is mounted on the balloon. Do not place excessive pressure on the device during crimping.

- Use of 2 inflation devices (1 for each balloon) with pressure gauges is highly recommended during this procedure when inflating the balloon to deliver the valve.
- The TPV is rigid and may make navigation through vessels difficult.
- Balloon deployment should be conducted under fluoroscopic guidance with appropriate X-ray equipment.
- Ensure the balloons are completely deflated before pulling the catheter back into the sheath.
- If resistance is felt upon attempted removal of the Ensemble™ transcatheter valve delivery system, ensure that both balloons have deflated completely and that there is no rupture of either the inner or outer balloons. This can be easily detected by the presence of blood in the balloon. If this occurs, maintain guidewire position and gently withdraw the delivery system using a twisting action under fluoroscopic observation. If the balloon catheter has seized the guidewire and cannot be withdrawn, then a second venous line should be inserted, and a catheter directed through the expanded Melody™ TPV, and a second guidewire placed in the pulmonary artery. The original Ensemble™ transcatheter valve delivery system and guidewire can then be carefully removed together under fluoroscopic guidance.

5.0 Potential Adverse Events

Potential procedural complications that may result from 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 (TIA, 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

[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.

6.0 Patient Information

6.1 Anticoagulation/Antiplatelet Information

Patients may require anticoagulation and/or antiplatelet therapy for an indefinite time period based on each patient's condition and physician recommendation.

Alternative antiplatelet/anticoagulation therapy should be considered for patients with known allergies to aspirin or heparin.

6.2 Identification and Management of Stent Fractures

The potential for stent fracture should be considered in all patients who undergo TPV placement, regardless of the previously discussed or subsequently characterized risk factors.

Identification

For patients found to have a substantial increase in the degree of RVOT obstruction, the possibility of an associated stent fracture should be considered and evaluated. Radiographic assessment of the stent with chest radiography or fluoroscopy should be included in the routine postprocedural evaluation of patients who receive a TPV.

Management

If a stent fracture is detected, continued monitoring of the stent should be performed in conjunction with clinically appropriate hemodynamic assessment. In patients with stent fracture and significant associated RVOT obstruction or regurgitation, reintervention should be considered in accordance with usual clinical practice.

Reintervention may include implantation of an additional Melody™ TPV or surgical conduit replacement. Note that limited data are available in the Melody™ US Clinical Study on reimplantation of another Melody™ TPV within the original Melody™ TPV (Section 10.0).

6.3 Endocarditis

Endocarditis is a potential adverse event associated with all bioprosthetic valves (Section 5.0). Patients should make their health care providers aware that they have a bioprosthetic valve before any procedure.

A low incidence of suspected endocarditis has been reported in patients implanted with the Melody™ TPV (Section 10.0). Unexplained, prolonged fever may be an indication of infection, and patients with these conditions should be advised to seek medical attention.

Prophylactic antibiotic therapy is recommended for patients implanted with a Melody™ TPV undergoing dental procedures.

6.4 Registration Information

A patient registration form is included in each TPV package. After implantation, please complete all requested information. The serial number is located on both the package and the identification tag attached to the TPV. Return the original form to the Medtronic address

indicated on the form and provide the temporary identification card to the patient prior to discharge.

Medtronic will provide an Implanted Device Identification Card to the patient. The card contains the name and telephone number of the patient's physician as well as information that medical personnel would require in the event of an emergency. Patients should be encouraged to carry this card with them at all times.

6.5 MRI Safety Information

Nonclinical testing and modeling has demonstrated that the Melody™ TPV is MR Conditional. A patient with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 1.5 T and 3 T
- Maximum spatial gradient magnetic field of 2500 gauss/cm (25 T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2.0 W/kg for 15 minutes of scanning (Normal Operating Mode)

Based on nonclinical testing and modeling, under the scan conditions defined above, the Melody™ TPV is expected to produce a maximum in vivo temperature rise of less than 2.1°C after 15 minutes of continuous scanning.

MR image quality may be compromised if the area of interest is in the same area, or relatively close to the position of the device. In nonclinical testing, the image artifact caused by the device extends approximately 3 mm from the Melody™ TPV when imaged with a spin echo pulse sequence and 6 mm when imaged with a gradient echo pulse sequence and a 3 T MRI System. The lumen of the device was obscured.

The presence of other implants or medical circumstances of the patient may require lower limits on some or all of the above parameters.

7.0 How Supplied

7.1 Packaging

The TPV is chemically sterilized and provided **sterile** and **nonpyrogenic** in a sealed glass container with a screw cap. Sterility is compromised if each tamper-evident seal is broken, the container is damaged, or leakage is evident. The outside of the container is **nonsterile** and should not be placed in the sterile field. The Ensemble™ transcatheter valve delivery system is sterilized with ethylene oxide gas and packaged in sterile, double aseptic transfer pouches. The delivery system is sterile if the pouches are undamaged and unopened. The outer surfaces of the outer pouch are **nonsterile** and must not be placed in the sterile field.

7.2 Storage

Store the TPV at 15°C to 25°C (59°F to 77°F). Store the Ensemble™ transcatheter valve delivery system at room temperature and away from direct sunlight. Appropriate inventory control should be maintained so that valves and delivery systems with the earliest Use By dates are preferentially implanted to avoid expiration.

8.0 Instructions for Use

The following is a sequential outline of the catheterization/implant procedure. The type of diagnostic catheters, guidewires, dilation balloons, sizing balloons, or other tools needed is at the discretion of the operator.

8.1 Access Site Preparation and Preimplant Diagnostics

1. Perform sterile preparation and draping of the access site.
2. Gain arterial and venous access.
3. Administer heparin to achieve a target ACT of >250 seconds.
4. Introduce a catheter into the arterial sheath and advance into the ascending aorta. Perform an aortogram to demonstrate the coronary arteries are not adjacent to the RVOT and that there is no risk of coronary compression when a stent or a Melody™ valve is implanted.

   If the coronaries appear to be in close proximity to the implant site, and coronary compression appears to be possible, further investigations should be done before moving forward with valve implantation.
5. Advance an angiographic catheter to the right ventricle (RV) or proximal part of the RVOT for angiography. The angiographic projections obtained will be based on the relative position of the RVOT.
6. Obtain angiographic measurements of the intended implantation site to assess suitability of the conduit for TPV implantation. If the angiographic measurements are unclear or if there is question of the conduit being compliant, a low-pressure sizing balloon (<811 kPa [<8 atm]) may be used to further assess the current condition of the conduit. If the narrowest conduit dimension (usually in the lateral projection) is ≤18 mm and less than the original conduit diameter, predilate the site of conduit obstruction (the implantation site) to facilitate optimal relief of conduit obstruction. The size of the predilation balloon should be at least 2 mm greater than the narrowest diameter of the conduit in any projection, no more than 110% of the nominal conduit diameter, and ≤20 mm for Melody™ TPV catalog number PB1016 and ≤22 mm for Melody™ TPV catalog number PB1018. Perform another conduit angiogram to ensure the conduit is intact. If there is no conduit injury, repeat the predilation steps, using the same guidelines with increasingly larger balloons until appropriate implant diameter has been reached.

   Note: If obstruction is noted, further preparation of the implantation site (eg, predilation) may be required to facilitate optimal relief of obstruction prior to implanting the Melody™ TPV.
7. Perform final sizing using a balloon diameter that clearly demonstrates the narrowest portion of the conduit (at a pressure of <811 kPa [<8 atm]). If the coronary arteries are an acceptable distance from the implant site and the prepared waist is ≥14 mm and ≤20 mm, the anatomy is consisted suitable for Melody™ TPV catalog number PB1016 implantation. If the coronary arteries are an acceptable distance from the implant site and the prepared waist is ≥14 mm and ≤22 mm, the anatomy is considered suitable for Melody™ TPV catalog number PB1018 implantation.

If questions about the coronary anatomy remain, repeat an aortic root angiogram or perform a selective coronary angiogram of the coronary system close to the conduit while simultaneously inflating the sizing balloon or largest predilation balloon to full expansion. If a coronary artery appears to be compressed by the balloon, the subject has unsuitable anatomy for the TPV, and the procedure should be abandoned.

8. Place a guidewire across the RVOT with its tip located as far distal in the pulmonary arterial bed as possible. Remove the diagnostic catheter. Leave the dilator in place and prepare the TPV and the delivery system.

8.2 Preparation of the TPV

To open the jar and rinse the TPV:

1. Before opening, carefully examine the jar and lid for damage, leakage, or broken seals. **The jar should contain enough sterilant to cover the TPV. Rinse the TPV for a minimum of 2 minutes to reduce the glutaraldehyde concentration from the TPV as directed in the following steps.**
    a. Using aseptic technique, prepare 3 sterile bowls; 1 remaining empty and 2 containing isotonic saline solution (500 mL) for rinsing.
    b. Using aseptic technique, remove the TPV by grasping the serial number tag with atraumatic forceps and lifting it from the jar. The outside of the jar is **nonsterile**. Do not allow the TPV to come into contact with the outside of the jar.
    c. A serial number tag is sutured to the outflow aspect of the TPV. Verify that the serial number on the tag matches the jar label serial number and the serial number on the patient registration form. If any differences in serial number are noted, do not use the TPV. Do not detach the tab from the TPV until implantation is imminent.
    d. Drain the residual storage solution from the valve into the empty discard bowl (bowl 1) by holding the TPV with the serial tag (outflow) downward.
    e. Transfer the empty TPV to the rinse bowl (bowl 2). Fill the TPV with rinse solution and alternately empty and fill by inverting and swirling, emptying and filling the valve for 1 minute, then empty the solution from the valve into the bowl.
    f. Transfer the empty TPV to the rinse bowl (bowl 3) and repeat step e for a minimum of 1 minute. Leave the TPV in the rinse bowl until implantation is imminent to prevent the tissue from drying.
    g. Empty the rinse solution from the TPV before loading the TPV on the delivery system.
2. Remove the serial number tag by cutting the suture attaching the tag to the valve.

8.3 Delivery System Loading and Placement of the TPV

1. Carefully examine the delivery system to confirm it was not damaged in shipment, and the balloon size is suitable for the intended procedure. The size of the delivery system to be used is based on the prepared implant site, as described in step 7 of Section 7.1, measuring ≥14 mm and ≤22 mm. The delivery system used should contain a TPV delivery balloon that is 0 to 2 mm larger than the waist at the implant site, but no more than 110% of the nominal conduit diameter.
2. Flush the delivery system guidewire lumen and the side port. Prepare the balloons by completely deflating with a fluid-filled syringe. Connect inflation syringes to the inner and outer balloon lumens. Inflation devices with pressure monitoring capabilities are recommended. Use a solution ratio of one-third to two-thirds contrast to saline in the inflation syringes.
3. Reduce the size of the valve while crimping it using mandrels of decreasing size. It is recommended to use a 2.5-mL sterile syringe for crimping to an intermediate size prior to final crimping onto the balloon catheter. When reduced to the intermediate size, slide the valve over the tip of the delivery system and center over the balloons.
4. Verify that the outflow end of the valve is oriented toward the distal end of the catheter. The outflow of the valve can be detected by the blue suture used to attach the valve at this location.
5. Gently crimp the valve onto the balloon using finger pressure and a rolling action to exert equal pressure on all sides of the valve, elongating the stent. Crimp only until no movement is felt on the catheter. AVOID BENDING OR TWISTING THE STENT. **Ensure the blue suture is adjacent to the blue tip of the catheter to ensure proper orientation of the valve for delivery.**
6. Carefully slide the sheath over the valve and balloons, ensuring that the crowns at the inflow end of the valve do not get caught on the sheath as it is advanced over the valve.

   Note: Check to ensure that the blue suture is adjacent to the blue tip of the delivery system.
7. Flush the sheath using the sidearm to remove air from the delivery system. Continue advancing the sheath and flushing until the sheath fits snugly over the proximal end of the blue tip.
8. Remove the venous dilator from the access site, and advance the delivery system over the guidewire. Carefully introduce the delivery system through the skin and advance toward the implantation site. Should bleeding be noted at the venous access site, advance the sleeve on the proximal end of the shaft into the vein to stop the bleeding. Advance the delivery system to the site where the valve is intended to be deployed. This requires manipulations of the delivery system and the guidewire. **Maintain adequate guidewire position at all times.**
9. Uncover the TPV once it has reached the level of the implantation site. Hold the shaft of the delivery system in place while pulling back on the outer sheath. The TPV is fully uncovered when the flushing port of the outer sheath is aligned with the proximal marker

on the catheter shaft. While uncovering, ensure that there is no inadvertent movement of the valve, which could possibly lead to the loss of the appropriate TPV position.

10. Once the TPV is fully uncovered, connect a syringe with pure contrast to the flush port of the delivery system. Inject a small amount of contrast to confirm good position of the valve and full retraction of the sheath. Further minor adjustments of the position of the TPV are still possible at this point.
11. Inflate the inner balloon followed by the outer balloon. Once the TPV is properly deployed against the implantation site, deflate the balloons and carefully remove the delivery system.
12. Measure the RV-PA pressure. If a significant gradient exists, perform balloon dilation with a high pressure balloon in order to minimize the gradient.
13. Compare the RV pressure with the systemic pressure measured through the arterial approach.
14. Perform a contrast injection into the proximal main PA (or distal RVOT) to demonstrate valve function and position. Ensure that the TPV is not held open by the guidewire and the catheter as this would give the false impression of pulmonary regurgitation.
15. Remove the catheters, guidewires, and sheaths and obtain hemostasis.

    Note: The delivery system is for single use and should only be inflated once. Do not use the delivery system to expand the valve after initial implantation. The TPV may be expanded after placement using a different balloon catheter. To minimize the risk of creating regurgitation, do not exceed the maximum recommended size of 20 mm for Melody™ TPV catalog number PB1016 and 22 mm for Melody™ TPV catalog number PB1018.

    Note: Circumferential tearing of the delivery balloon catheter prior to complete expansion of the valve may cause the balloon to become tethered to the TPV, requiring surgical removal. In case of rupture of an adequately sized balloon after stent expansion, the balloon can be withdrawn and a new balloon catheter can be exchanged over a guidewire to complete expansion of the TPV.

Table 1: Melody™ TPV Sizing Chart

Delivery System Size – Inner Balloon / Outer Balloon	Inner Balloon Maximum Applied Pressure (RBP)		Outer Balloon Applied Pressure		Corresponding Valve Outside Diameter (mm) (balloon inflated)
	atm	**kPa**	**atm**	**kPa**	
Size 18 mm Inner: 9 mm × 3.5 cm / Outer: 18 mm × 4 cm	5	506	1	101	17.9
			2	203	18.6
			3	304	19.4
			4 (RBP)	**405**	**20.1**
Size 20 mm Inner: 10 mm × 3.5 cm / Outer: 20 mm × 4 cm	5	506	1	101	19.7
			2	203	20.7
			3	304	21.7
			4 (RBP)	**405**	**22.4**
Size 22 mm Inner: 11 mm × 3.5 cm / Outer: 22 mm × 4 cm	4.5	456	1	101	21.8
			2	203	22.8
			3 (RBP)	**304**	**24.1**

Notes:
1. Do not exceed bolded pressure values for either the inner or outer balloon of the delivery system size.
2. RBP = Rated Burst Pressure = Maximum Applied Pressure
3. atm = atmosphere
4. kPa = kilopascal

Table 2: Approximate Length of the TPV Following Deployment with the Corresponding Ensemble™ Delivery System

Expanded Outer Balloon OD Size	Reference TPV Length (crimped/loaded on delivery system)	Reference TPV Length (after balloon deflation)
18 mm	33 mm	26 mm
20 mm	32 mm	24 mm
22 mm	32 mm	21 mm

Note: Data on file

9.0 Return of Explanted TPV

Medtronic is interested in obtaining recovered explanted TPVs. Specific pathological studies of the explanted valve will be conducted under the direction of a consulting pathologist. A written summary of the findings will be returned to the physician upon request. To obtain a product return kit, contact a Medtronic distribution center or a Medtronic Representative. If a kit is not available, place the explanted valve in a container of glutaraldehyde or 10% buffered formalin immediately after excision. For further instructions on the return of an explanted device, contact a Medtronic Representative.

10.0 Clinical Studies

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

The Melody™ TPV Long-term Follow-up PAS is a prospective, nonrandomized, multicenter investigational study being 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 this clinical study is to confirm the long-term functionality of transcatheter implantation of the Medtronic Melody™ TPV in dysfunctional RVOT conduits.

The primary outcome measure is TPV dysfunction at 5 years after TPV implant, which is a composite outcome defined as RVOT reoperation for conduit dysfunction or device-related reasons, catheter reintervention on the TPV, or hemodynamic dysfunction of the TPV (moderate or greater pulmonary regurgitation, and/or a mean RVOT gradient greater than 40 mm Hg). The secondary outcome measures include (1) freedom from TPV dysfunction at 10 years; (2) procedural success; (3) safety including serious procedural adverse events, serious device-related adverse events, stent fracture, catheter reintervention on the TPV, surgical replacement of the RVOT conduit, and death (all-cause, procedural, and device-related); (4) Clinical utility (New York Heart Association [NYHA] classification).

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.

A total of 171 subjects were enrolled in this study between January 31, 2007 and January 12, 2010. The following data are interim results current through March 1, 2014. In total, 167 subjects underwent catheterization for potential implantation of the Melody™ TPV, with 150 subjects subsequently receiving the valve. The mean length of follow-up was 52.9 ± 15.6 months.

10.1.1 Subject Demographics

Table 3 presents the subject demographics and baseline characteristics analyzed for 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 3: Long-term Follow-up PAS: Subject Demographics/Baseline Data – 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	
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).

10.1.2 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 4. 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. Concomitant procedures were not allowed per the CIP in the first 35 subjects of the IDE trial. Following revision of the CIP to allow for concomitant procedures, pre-stenting of the RVOT was the most commonly performed concomitant procedure (n = 54).

Table 4: 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
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).

10.1.3 Safety Results

10.1.3.1 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. Three subjects experienced an RVOT conduit rupture or dissection, 2 subjects experienced a hemothorax, and 2 subjects had a vessel perforation.

Table 5: Long-term Follow-up PAS: Summary of Acute Procedure-related Serious Adverse Events – Catheterized Cohort (N = 167)

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)
Other respiratory/pulmonary	0.6% (1/167)
Other vascular access site complication	0.6% (1/167)

10.1.3.2 Device-related Adverse Events

Table 6 presents the incidence of device-related adverse events and freedom from event at 1 year, 3 years, and 5 years postimplant.

Table 6: 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)
Nonstructural 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 (CI) 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.

Concomitant Pre-stenting Procedure

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 physician. Thus, the data for the pre-stented cohort reported below represent the outcomes of subjects who were implanted with a variety (in number and type) of stents and the Melody™ TPV. Again, no particular number or types of stents were specified in the protocol, nor were there criteria for performing the pre-stenting procedure.

The Melody™ TPV was studied in pediatric and adult populations. In all, 54 of 115 (47.0%) implanted patients eligible for pre-stenting received concomitant pre-stenting of the RVOT conduit. From a retrospective analysis of the IDE cohort dataset, stratified by pre-stenting status (as shown in Table 7), one can observe that there were fewer instances of major fracture of the Melody™ TPV in the pre-stenting group. Note that this study was not designed to investigate the differences in outcomes between non–pre-stented and pre-stented groups nor was this study designed to investigate whether stents used to pre-stent the RVOT landing site are safe and effective for this use. More information is needed to determine whether there is a causal relationship between the pre-stenting procedure and the improvement in major fracture rate.

Table 7: Summary of Device-related Adverse Events During Follow-up by Pre-stenting Status – Implanted Cohort (N = 150)

Event	Subjects Without Pre-stenting With Event (N = 96)	Pre-stented Subjects With Event (N = 54)
Stent fracture (all)	42.7% (41/96)	14.8% (8/54)
Stent fracture: major with fragment embolization	20.8% (20/96) 1.0% (1/96)	5.6% (3/54) 0.0% (0/54)
Valve dysfunction: stenosis (all)	21.9% (21/96)	11.1% (6/54)
Valve dysfunction: regurgitation	1.0% (1/96)	0.0% (0/54)
Valve dysfunction: mixed	0.0% (0/96)	0.0% (0/54)
Valvular regurgitation, tricuspid	9.4% (9/96)	3.7% (2/54)
Prosthetic valve endocarditis	4.2% (4/96)	1.9% (1/54)
Pulmonary thromboembolism	1.0% (1/96)	0.0% (0/54)
Paravalvular leak: minor	1.0% (1/96)	0.0% (0/54)
Paravalvular leak: major	0.0% (0/96)	0.0% (0/54)
Structural deterioration of the TPV	0.0% (0/96)	0.0% (0/54)
Embolization of the TPV	0.0% (0/96)	0.0% (0/54)
Nonstructural dysfunction	0.0% (0/96)	0.0% (0/54)
Thrombosis of the TPV	0.0% (0/96)	0.0% (0/54)
Hemorrhage	0.0% (0/96)	0.0% (0/54)

Note: The term “stent fracture” refers to the fracture of the Melody™ TPV. However, in subjects with multiple

Event	Subjects Without Pre-stenting With Event (N = 96)	Pre-stented Subjects With Event (N = 54)
stents in the RVOT it is difficult to definitively attribute stent fractures to the Melody™ frame versus another stent.		

10.1.3.3 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 was required to prevent permanent impairment of a body function or permanent damage to a body structure (eg, reoperation, implantation of another TPV). Freedom from major stent fracture at 5 years postimplant was estimated to be 84.3%.

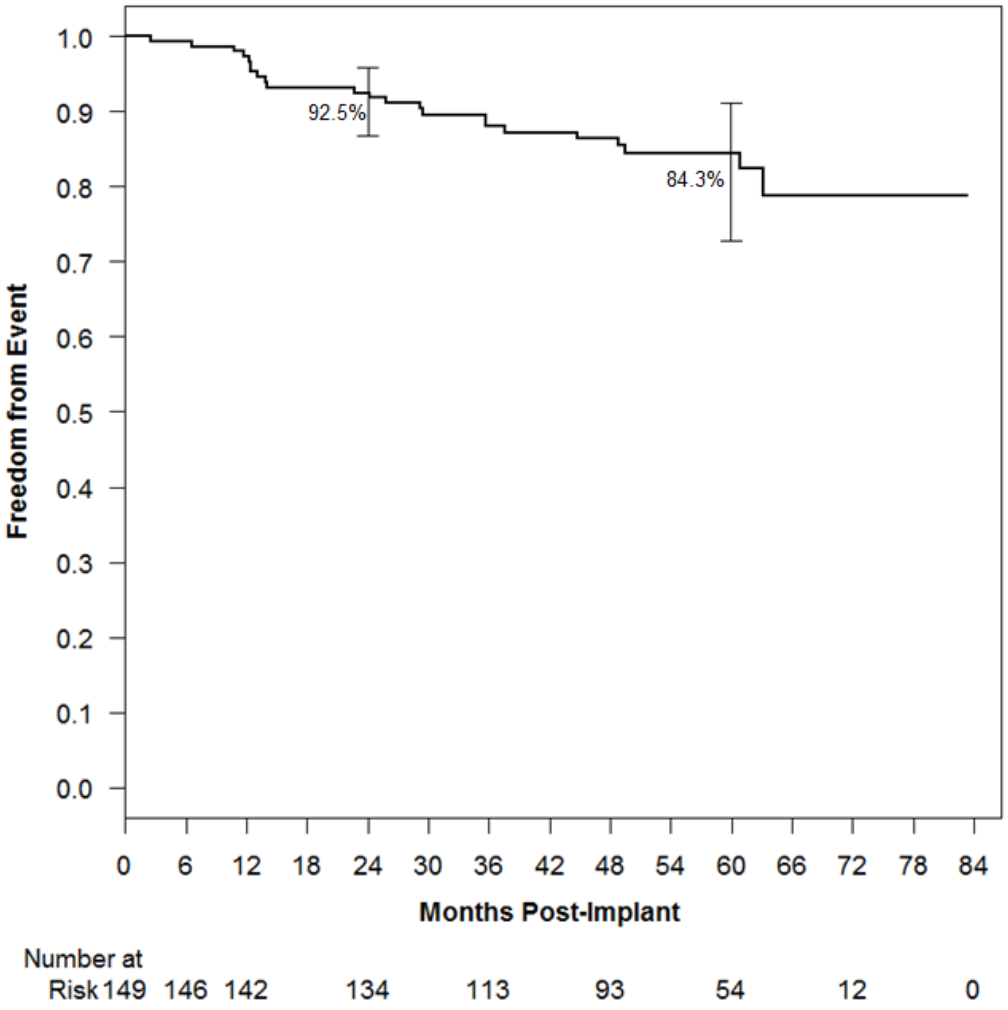

Figure 1: Kaplan-Meier Freedom From Major Stent Fracture – Implanted >24 hours Cohort (N = 149)

Notes:

1. The cumulative probability of event free estimate is based on the Kaplan-Meier (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.

10.1.3.4 Freedom From Prosthetic Valve Endocarditis

Freedom from prosthetic valve endocarditis at 5 years postimplant was estimated to be 96.1%. 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.

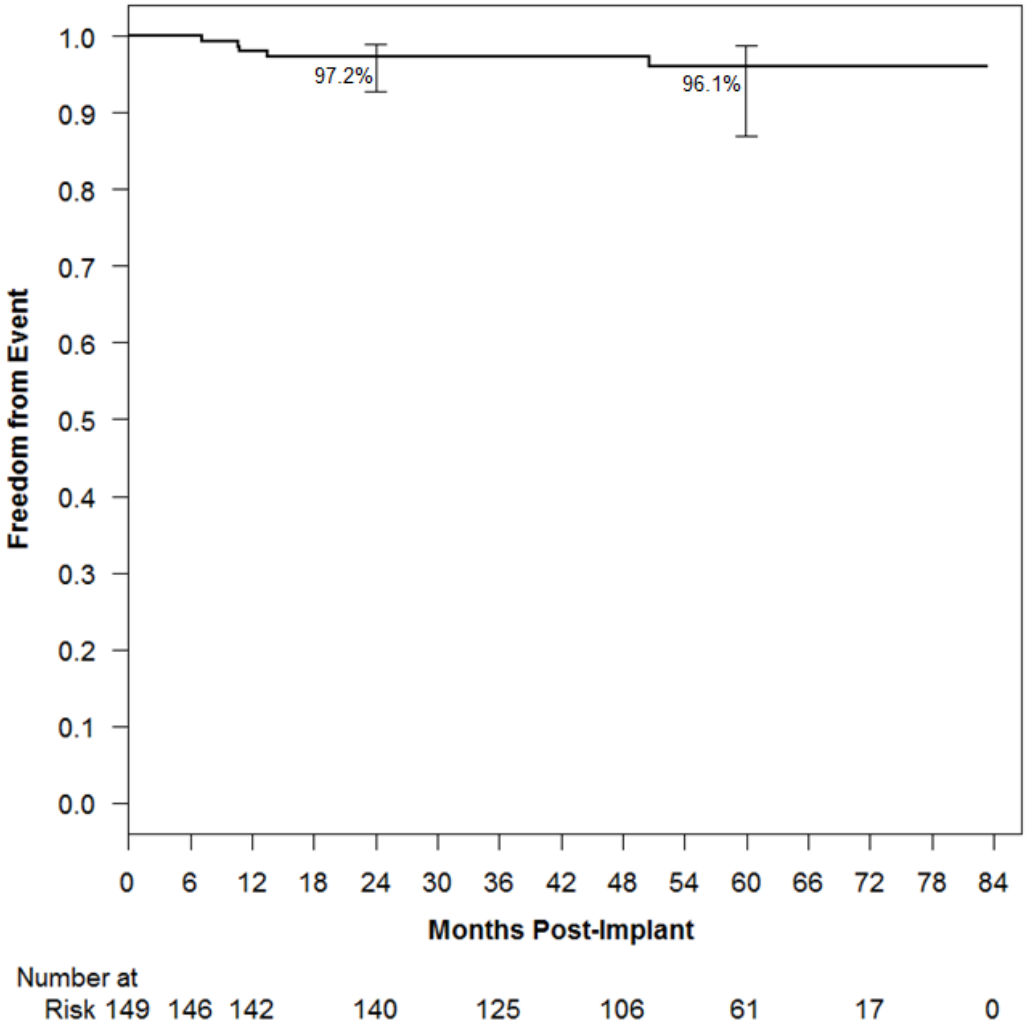

Figure 2: Kaplan-Meier Freedom From Prosthetic Valve Endocarditis – Implanted >24 Hours Cohort (N = 149)

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.

10.1.3.5 Freedom From All-cause Mortality

Freedom from all-cause mortality at 5 years postimplant was estimated to be 97.1%. There were 5 deaths during follow-up, 1 of which was early and was reported as possibly related to the procedure. There were 4 late deaths, 1 of which was reported as possibly device-related.

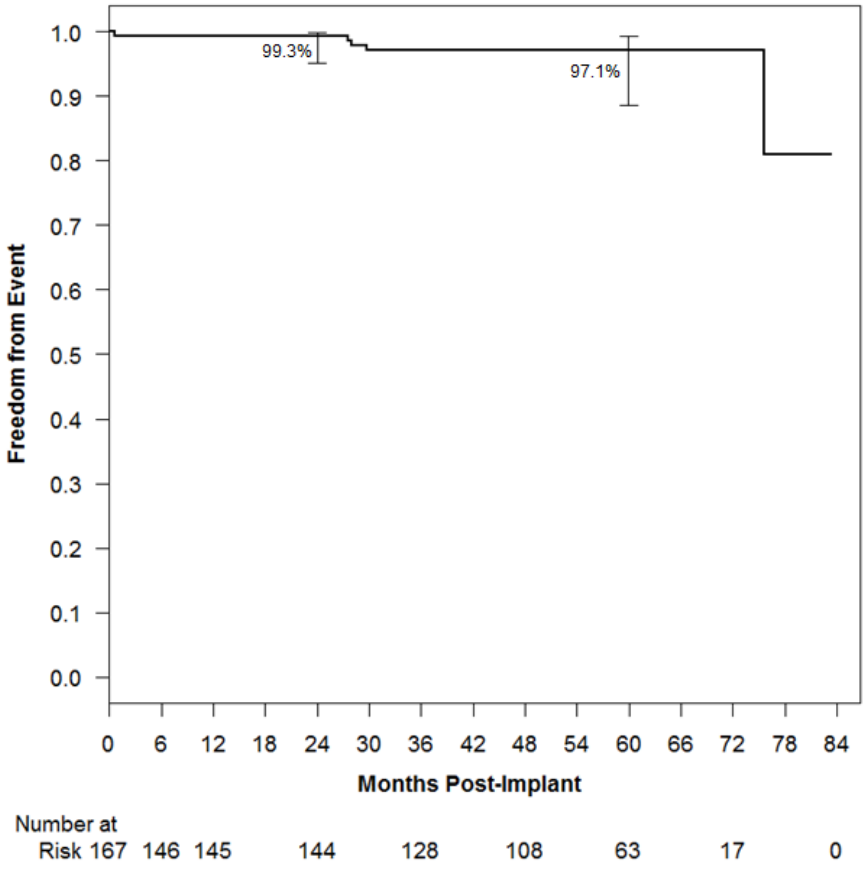

Figure 3: Kaplan-Meier Freedom From All-cause Mortality – Catheterized Cohort (N = 167)

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.

10.1.4 Effectiveness Results

10.1.4.1 Procedural Success

Acute procedural success was defined as the percentage of subjects attempted with the TPV fixated within the desired location, an RV-PA peak-to-peak gradient <35 mm Hg postimplant, less than mild pulmonary regurgitation by angiography postimplant, and free of explant at 24 hours postimplant. Of the 150 subjects with an attempted implant, 94.7% had a procedural success (n = 142) as shown in Table 8. All valves delivered remained in the desired implant location; however, 1 subject was explanted <24 hours after implant due to conduit rupture, 1 subject had a RV-PA peak-to-peak gradient >35 mm Hg, 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 8: 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%

10.1.4.2 Freedom From TPV Dysfunction

TPV dysfunction is a composite outcome, defined as RVOT conduit reoperation for device-related reasons, reintervention, or hemodynamic dysfunction of the TPV (moderate or greater pulmonary regurgitation, and/or mean RVOT gradient of >40 mm Hg). At 5 years, the freedom from TPV dysfunction was estimated to be 72.0%. Since TPV dysfunction is a composite outcome relying on echocardiographic assessment at each visit interval, the Kaplan-Meier (KM) rate at the end of the visit window is presented. 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 pulmonary regurgitation during follow-up which did not require intervention, and 1 subject was explanted due to heart failure and the need for a right ventricular assist device.

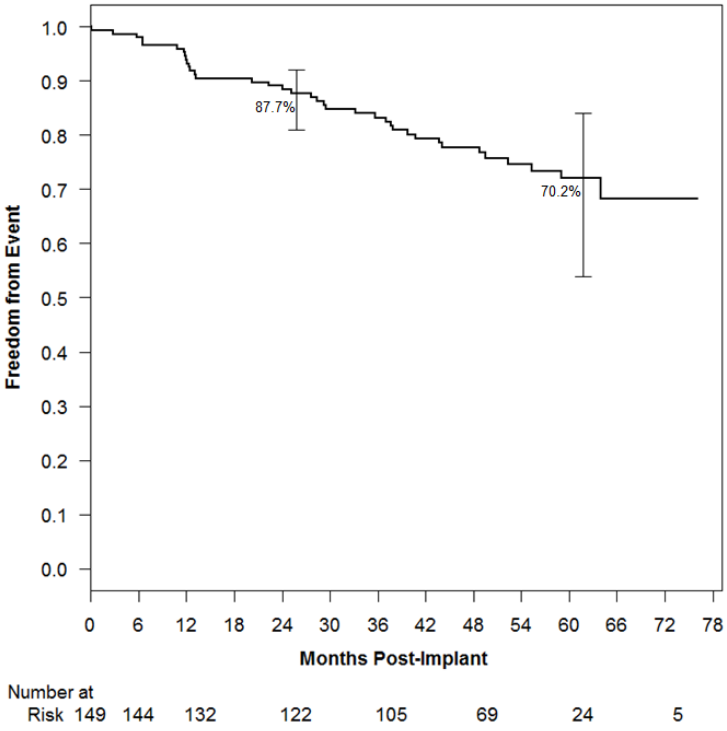

Figure 4: Kaplan-Meier Freedom From TPV Dysfunction – Implanted >24 hours Cohort (N = 149)

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 KM rate at the end of the visit window is presented.

10.1.4.3 Freedom From RVOT Conduit Reoperation

At 5 years postimplant, the freedom from RVOT conduit reoperation was estimated to be 91.7%. Eleven subjects underwent RVOT conduit reoperation during follow-up. The primary 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 prior to surgical explant.

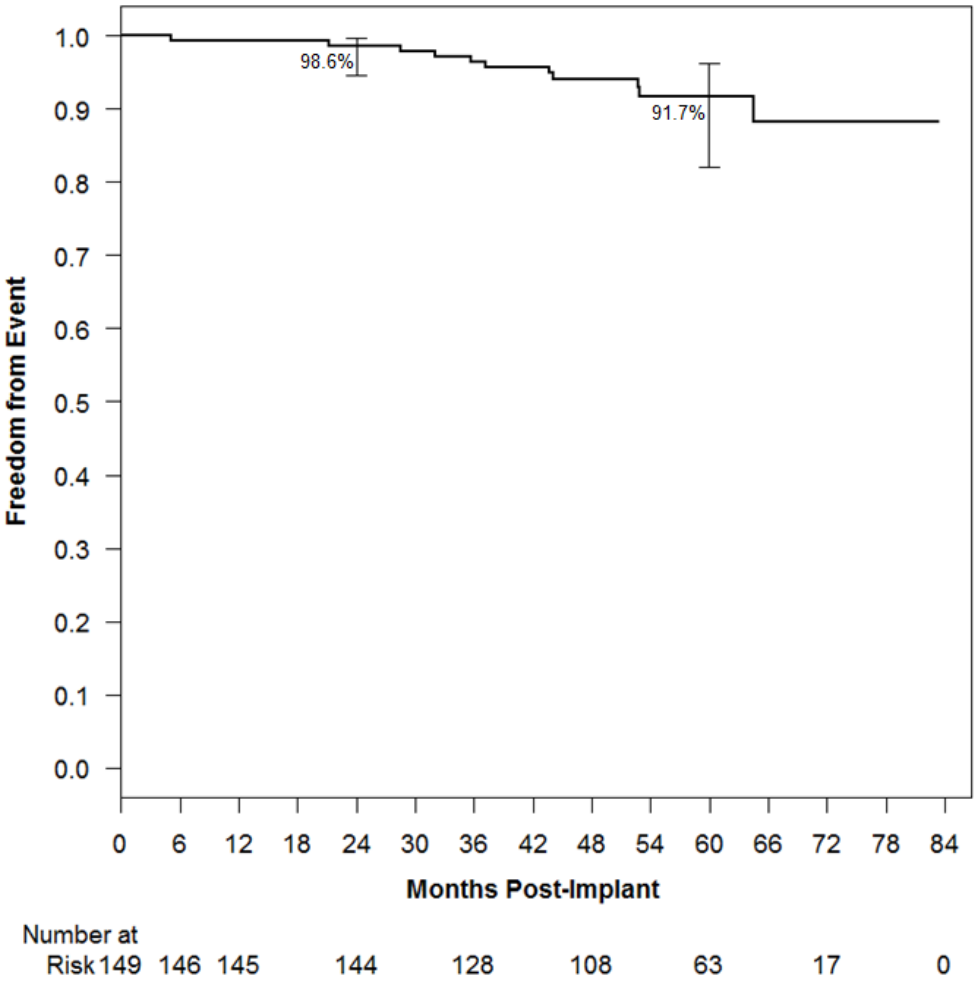

Figure 5: Kaplan-Meier Freedom From RVOT Conduit Reoperation – Implanted >24 hours Cohort (N = 149)

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.

10.1.4.4 Freedom From Catheter Reintervention on the TPV

Freedom from catheter reintervention at 5 years postimplant was estimated to be 79.5%. The most common need for reintervention was stenosis. Twenty subjects received a subsequent Melody™ TPV, with or without bare metal stenting; one of these subjects went on to receive a third Melody™ TPV while 2 others were subsequently explanted. Five subjects underwent balloon angioplasty and 1 subject underwent bare metal stenting for stenosis and was subsequently explanted due to clinically significant pulmonary regurgitation (PR).

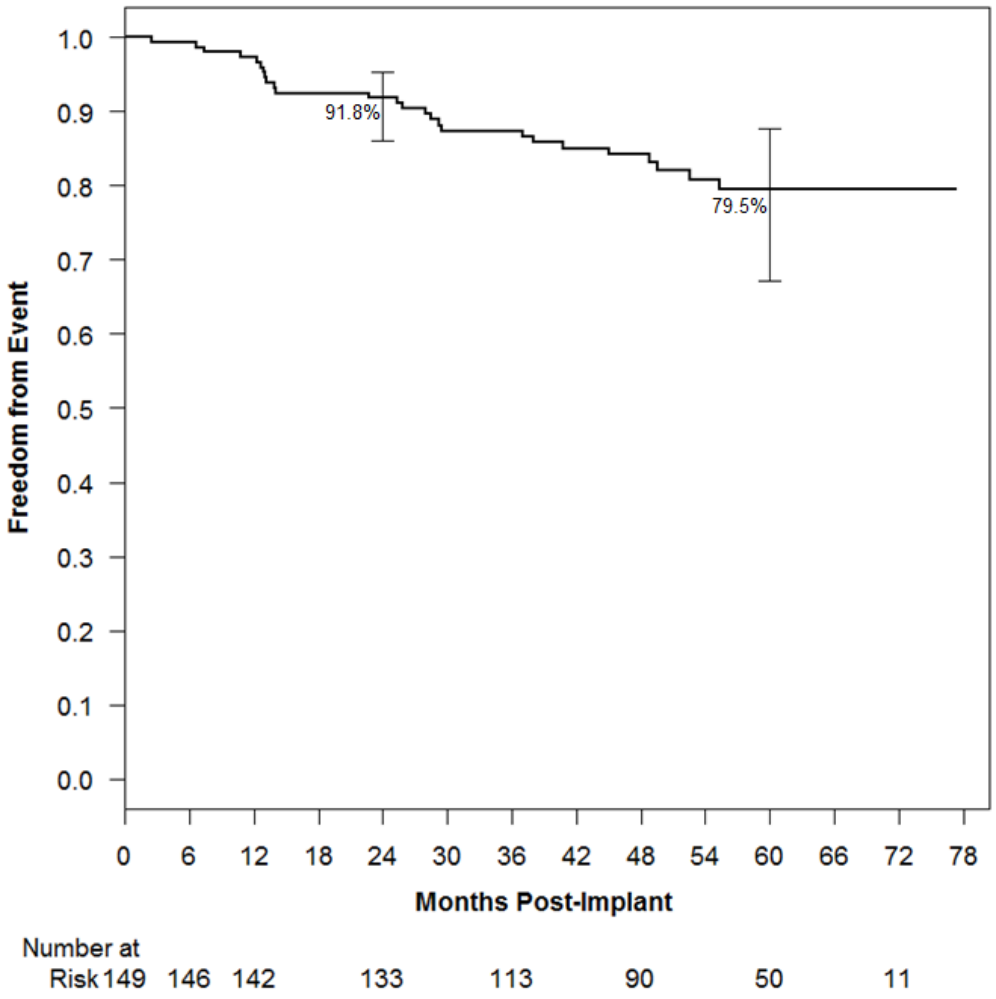

Figure 6: Kaplan-Meier Freedom From Catheter Reintervention on the TPV – Implanted >24 hours Cohort (N = 149)

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.

10.1.4.5 Hemodynamic Performance

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

Table 9: Long-term Follow-up PAS: Pulmonary Regurgitation by Time Interval – Implanted >24 Hours Cohort (N = 149)

Degree of Regurgitation[1, 2]	Preimplant (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 preimplant, 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 postimplant.

Average RVOT mean gradient was 17.7 ± 7.7 mm Hg at discharge and remained clinically stable throughout follow-up, as shown in Table 10.

Table 10: Long-term Follow-up PAS: RVOT Mean Gradient by Time Interval – Implanted >24 Hours Cohort (N = 149)

RVOT Mean Gradient[1, 2]	Preimplant (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 preimplant, 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 postimplant.

10.1.4.6 NYHA

Figure 7 presents the NYHA functional class of subjects throughout follow-up. Preimplant, the majority of patients were NYHA Class II. Following Melody™ TPV implant and throughout follow-up, the majority of subjects were in class I.

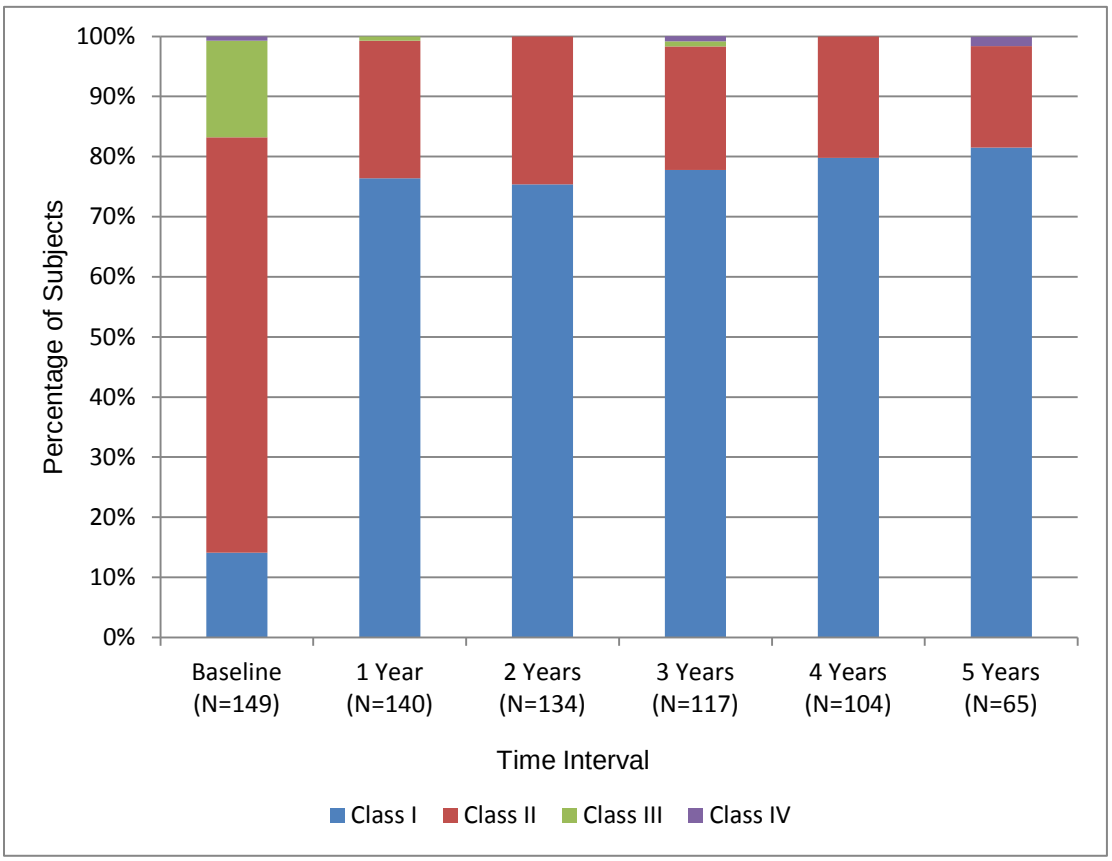

Figure 7: New York Heart Association Classification – Implanted >24 hours Cohort (N = 149)

10.2 Melody™ TPV New Enrollment PAS

Following HDE approval of the Melody™ TPV in 2010, a New Enrollment PAS was initiated as a condition of approval study involving 10 new centers in the United States. It is a prospective, nonrandomized, multicenter evaluation to confirm the short-term hemodynamic effectiveness of implantation of the Medtronic Melody™ TPV achieved by real-world providers is equivalent to the historical control established in the five center IDE study.

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 is less than or equal to 30 mm Hg as measured by CW Doppler, severity of pulmonary regurgitation is less than moderate by Doppler echocardiography, and free from RVOT conduit reoperation and catheter reintervention at 6 months after TPV implantation. The secondary 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 postimplant; (4) freedom from stent fracture; (5) freedom from reintervention 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.

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

A total of 131 subjects were enrolled in this study between July 29, 2010 and July 12, 2012. The following data are interim results current through March 1, 2014. In total, 120 subjects underwent catheterization for potential implantation of the Melody™ TPV; of these, 101 subjects had an implant attempt, and 100 subjects subsequently received the valve. The mean length of follow-up was 25.1 ± 9.4 months.

10.2.1 Subject Demographics

Table 11 presents the subject demographics and baseline characteristics analyzed for 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 11: 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) when originally implanted	
n	113
Mean ± SD	20.9 ± 3.4
Median [Min, Max]	21.0 [8.0, 30.0]
Bioprosthesis size (mm) when originally implanted	
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).

10.2.2 Procedural Data

A summary of procedural data is provided in Table 12. 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 12: 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 pulmonary artery (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 atrial septal defect (ASD) or patent foramen ovale (PFO)	0.0% (0/120)
Closure of ventricular septal defect (VSD)	0.0% (0/120)
Other[3]	8.3% (10/120)
Length of hospital stay (days)	
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 New Enrollment PAS protocol.
[2] Subjects may have had more than one concomitant procedure performed.
[3] Other concomitant procedures included: balloon angioplasty of conduit (n = 5), dilation of left pulmonary artery (LPA) or right pulmonary artery (RPA) stents (n = 2), balloon angioplasty of the proximal LPA (n = 1), left ventricular assist device placed (n = 1), pulmonary valvuloplasty (n = 1).

10.2.3 Safety Results

10.2.3.1 Acute Procedure-related Adverse Events

Of the 120 subjects catheterized, 10 (8.3%) experienced acute (day of catheterization) serious adverse events classified as either possibly or definitely related to the procedure.
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 13: 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)

10.2.3.2 Device-related Adverse Events

Table 14 presents the incidence of device-related adverse events and freedom from event at 1 years and 2 years postimplant. 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 14: 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[3]	1.0% (1/100)	100.0% (NA)	100.0% (NA)
Embolization of the TPV	0.0% (0/100)	100.0% (NA)	100.0% (NA)
Nonstructural 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.

Concomitant Pre-stenting Procedure

The protocol for the New Enrollment PAS of the Melody™ TPV allowed for concomitant vascular interventional procedures during the Melody™ TPV procedure. Pre-stenting of the RVOT landing site for the Melody™ TPV was one concomitant procedure performed during the New Enrollment PAS. 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 physician. Thus, the data for the pre-stented cohort reported below represent the outcomes of subjects who were implanted with a variety (in number and type) of stents and the Melody™ TPV. Again, no particular number or types of stents were specified in the protocol, nor were there criteria for performing the pre-stenting procedure.

The Melody™ TPV was studied in pediatric and adult populations. Seventy-six (76) out of the 100 New Enrollment PAS subjects implanted were pre-stented. From a retrospective analysis of the New Enrollment PAS cohort dataset, stratified by pre-stenting status (as shown in Table 15), one can observe that there were fewer instances of major fracture of the Melody™ TPV in the pre-stenting group. Note that this study was not designed to investigate the differences in outcomes between non–pre-stented and pre-stented groups nor was this study designed to investigate whether stents used to pre-stent the RVOT landing site are safe and effective for this use. More information is needed to determine whether there is a causal relationship between the pre-stenting procedure and the improvement in major fracture rate.

Table 15: Summary of Device-related Adverse Events During Follow-up by Pre-stenting Status – Implanted Cohort (N = 100)

Event	Subjects Without Pre-stenting With Event (N = 24)	Pre-stented Subjects With Event (N = 76)
Stent fracture (all)	4.2% (1/24)	18.4% (14/76)
Stent fracture: major	4.2% (1/24)	3.9% (3/76)
with fragment embolization	0.0% (0/24)	1.3% (1/76)
Valve dysfunction: stenosis (all)	8.3% (2/24)	9.2% (7/76)
Valve dysfunction: regurgitation	4.2% (1/24)	3.9% (3/76)
Valve dysfunction: mixed	0.0% (0/24)	2.6% (2/76)
Prosthetic valve endocarditis	4.2% (1/24)	7.9% (6/76)
Paravalvular leak: minor	4.2% (1/24)	0.0% (0/76)
Paravalvular leak: major	0.0% (0/24)	1.3% (1/76)
Pulmonary thromboembolism	0.0% (0/24)	1.3% (1/76)
Valvular regurgitation, tricuspid	0.0% (0/24)	1.3% (1/76)
Structural deterioration of the TPV	0.0% (0/24)	1.3% (1/76)
Nonstructural dysfunction	0.0% (0/24)	0.0% (0/76)
Thrombosis of the TPV	0.0% (0/24)	0.0% (0/76)
Hemorrhage	0.0% (0/24)	0.0% (0/76)
Embolization of the TPV	0.0% (0/24)	0.0% (0/76)

Note: 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.

10.2.3.3 Freedom From Major Stent Fracture

Stent fracture was defined as any visual evidence on radiography or at explant of loss of contact between elements (cells) of the stent. Major stent fracture includes those where intervention was required to prevent permanent impairment of a body function or permanent damage to a body structure (eg, reoperation, implantation of another TPV). Freedom from major stent fracture at 3 years postimplant was estimated to be 90.3%.

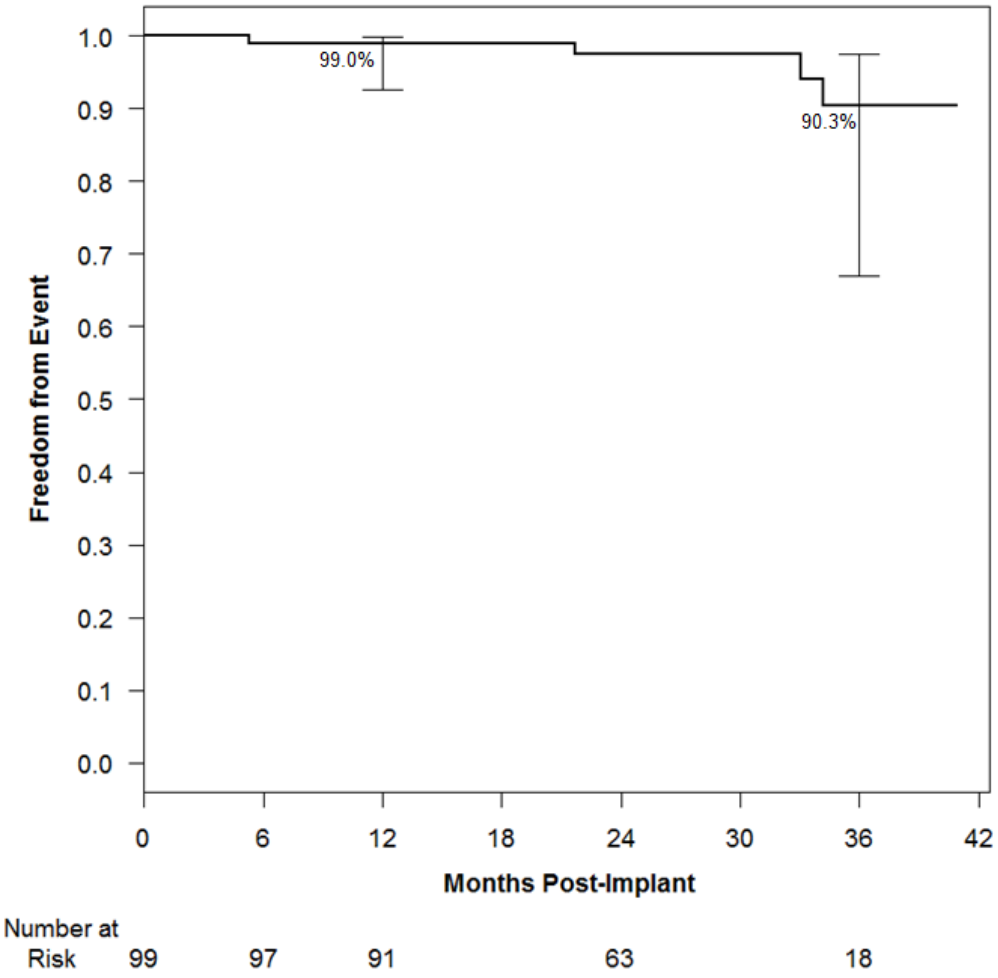

Figure 8: Kaplan Meier Freedom from Major Stent Fracture – Implanted >24 hours Cohort (N = 99)

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.

10.2.3.4 Freedom From Prosthetic Valve Endocarditis

Freedom from prosthetic valve endocarditis at 3 years postimplant was estimated to be 91.2%. Seven subjects were reported to have prosthetic valve endocarditis. Three subjects were treated with antibiotics, 3 had the TPV explanted, and 1 subject died 10 days after diagnosis of endocarditis.

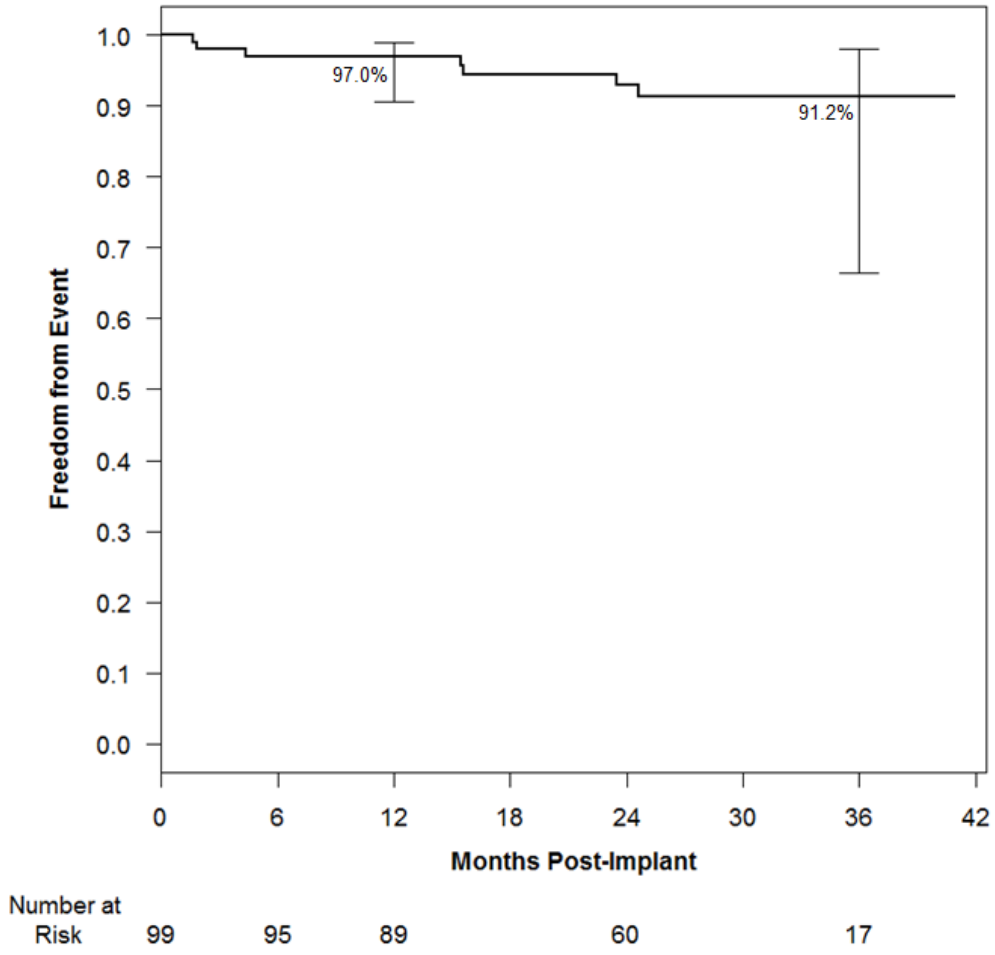

Figure 9: Kaplan-Meier Freedom From Prosthetic Valve Endocarditis – Implanted >24 Hours Cohort (N = 99)

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.

10.2.3.5 Freedom From All-cause Mortality

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

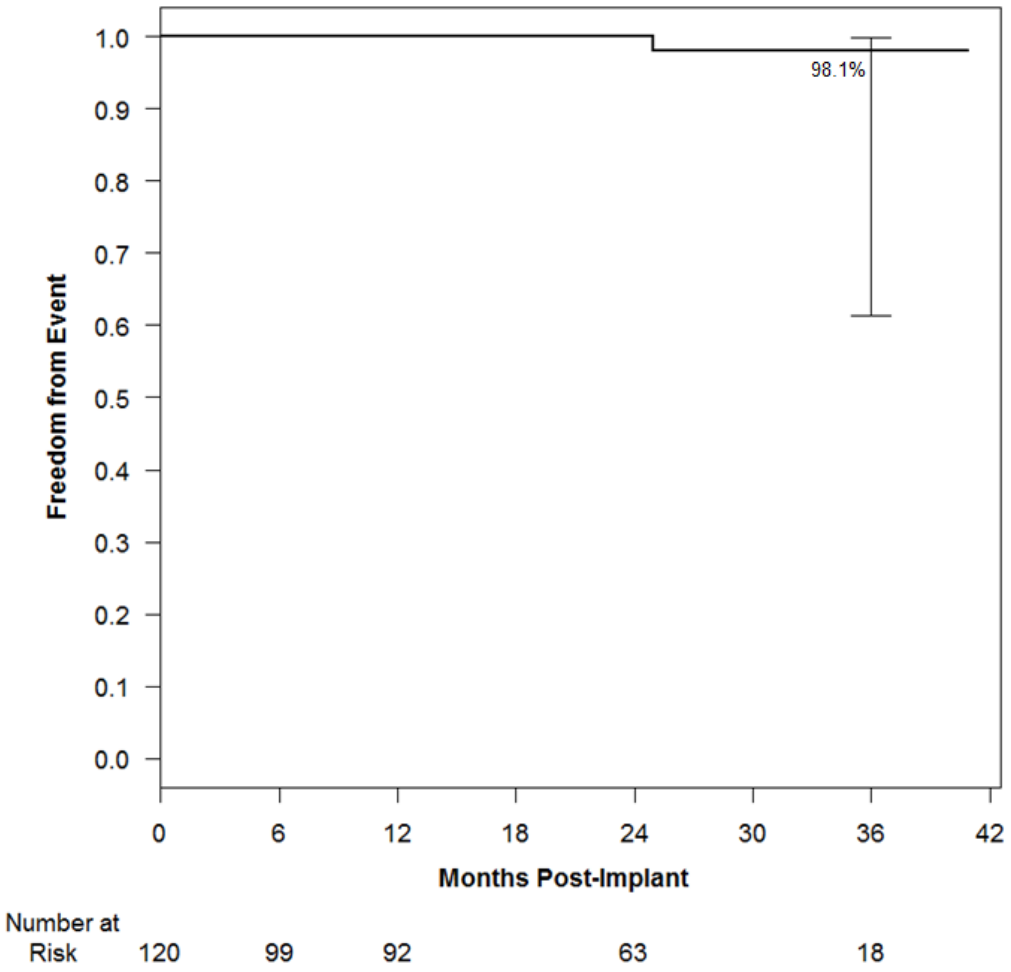

Figure 10: Kaplan-Meier Freedom From All-cause Mortality – Catheterized Cohort (N = 120)

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.

10.2.4 Effectiveness Results

10.2.4.1 Procedural Success

Acute procedural success was defined as the percentage of subjects attempted with the TPV fixated within the desired location, a peak-to-peak RV-PA gradient <35 mm Hg measured in the catheterization lab post-implantation, less than mild pulmonary regurgitation by angiography post-implantation, and free of explant at 24 hours post-implantation. Of the 101 subjects with an attempted implant, 92.1% met the criteria for procedural success (n = 93). Implant 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 16: 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%

10.2.4.2 Freedom From TPV Dysfunction

TPV dysfunction is a composite outcome, defined as RVOT conduit reoperation for device-related reasons, reintervention, or hemodynamic dysfunction of the TPV (moderate or greater pulmonary regurgitation, and/or mean RVOT gradient of >40 mm Hg). At 3 years postimplant, freedom from TPV dysfunction was estimated to be 65.1%. Since TPV dysfunction is a composite outcome relying on echocardiographic assessment at each visit interval, the KM rate at the end of the visit window is presented. Of the 17 subjects with TPV dysfunction throughout follow-up, 13 presented with stenosis, 6 of which were secondary to stent fracture, 4 cases of recurrent stenosis, and 3 secondary to endocarditis. Three subjects had moderate PR during follow-up, which did not require intervention, and 1 subject had their conduit replaced while undergoing aortic valve replacement.

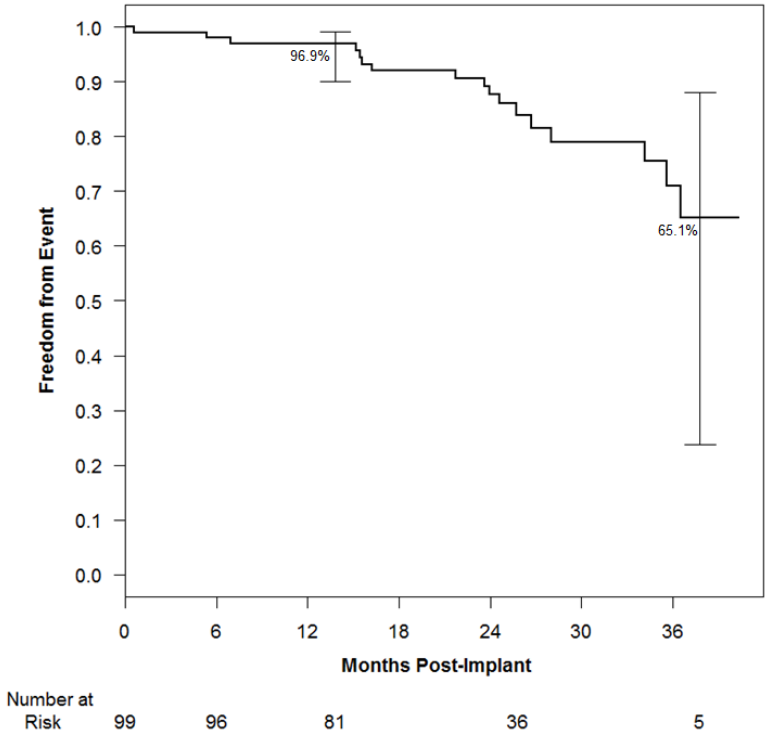

Figure 11: Kaplan-Meier Freedom From TPV Dysfunction – Implanted >24 hours Cohort (N = 99)

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 KM rate at the end of the visit window is presented.

10.2.4.3 Freedom From RVOT Conduit Reoperation

At 3 years postimplant, the freedom from RVOT conduit reoperation was estimated to be 78.9%. Ten subjects underwent RVOT conduit reoperation during follow-up. The primary 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.

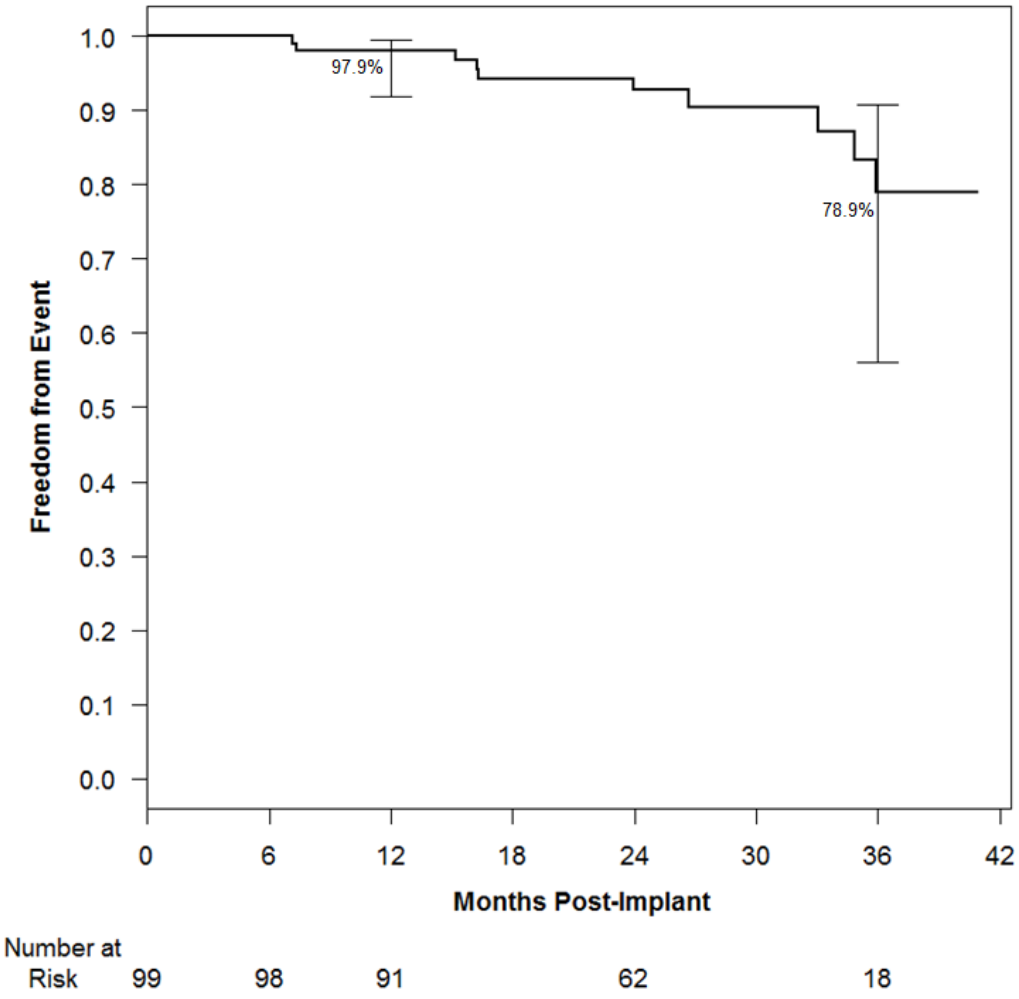

Figure 12: Kaplan-Meier Freedom From RVOT Conduit Reoperation – Implanted >24 hours Cohort (N = 99)

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.

10.2.4.4 Freedom From Reintervention on the TPV

Freedom from catheter reintervention at 3 years postimplant was estimated to be 93.3%. During follow-up 3 subjects had a catheter reintervention 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.

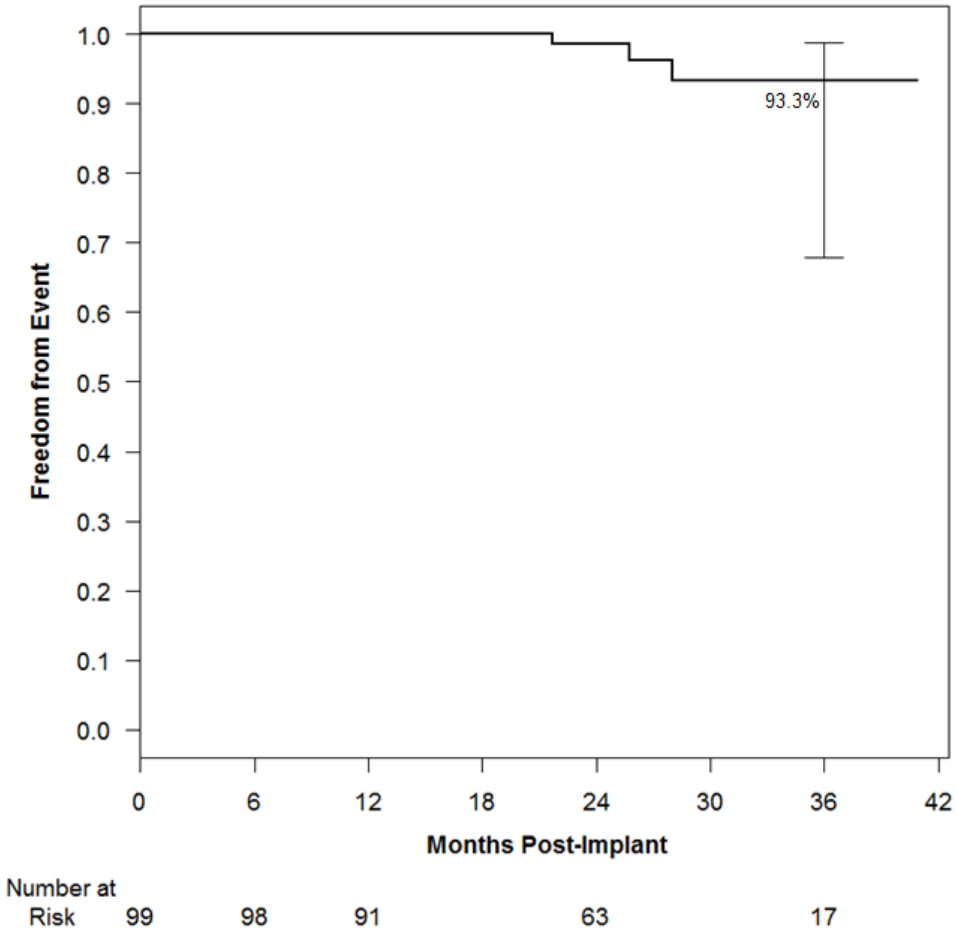

Figure 13: Kaplan-Meier Freedom From Catheter Reintervention on the TPV – Implanted >24 hours Cohort (N = 99)

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.

10.2.4.5 Primary Outcome Measures

The primary objective of the New Enrollment PAS was 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%).

Acceptable TPV hemodynamic function at six months after successful TPV implantation is determined as a composite of the following:

- Mean RVOT gradient is less than or equal to 30 mm Hg as measured by CW Doppler, and
- Severity of pulmonary regurgitation is less than moderate by Doppler echocardiography, and
- Free from RVOT conduit reoperation or catheter reintervention at 6 months after TPV implantation.

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 mm Hg. 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 Table 17, Table 18, and Table 19.

Table 17: 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 18: New Enrollment PAS: 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 19: New Enrollment PAS: 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	
99	96 (97.0%)	1.7%	92.4%	p-value	Objective Met
				<0.0001	Yes
Note: The p-value was from the exact test.					

10.2.4.6 Hemodynamic Performance

At discharge and throughout 3 years of follow-up, the majority of subjects had no more than mild PR and no subjects presented with severe PR. The average RVOT mean gradient was 16.3 ± 7.1 mm Hg at discharge and remained clinically stable throughout follow-up as shown in Table 20.

Table 20: New Enrollment PAS: Pulmonary Regurgitation by Time Interval – Implanted >24 hours Cohort (N = 99)

Degree of Regurgitation[1, 2]	Preimplant (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 preimplant, 3 subjects at discharge, 3 subjects at 6 months, 1 subject at 1 year, and 1 subject at 2 years postimplant.

Table 21: New Enrollment PAS: RVOT Mean Gradient by Time Interval – Implanted >24 hours Cohort (N = 99)

RVOT Mean Gradient[1, 2]	Preimplant (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
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 preimplant, 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 postimplant.

10.2.4.7 NYHA

Figure 14 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.

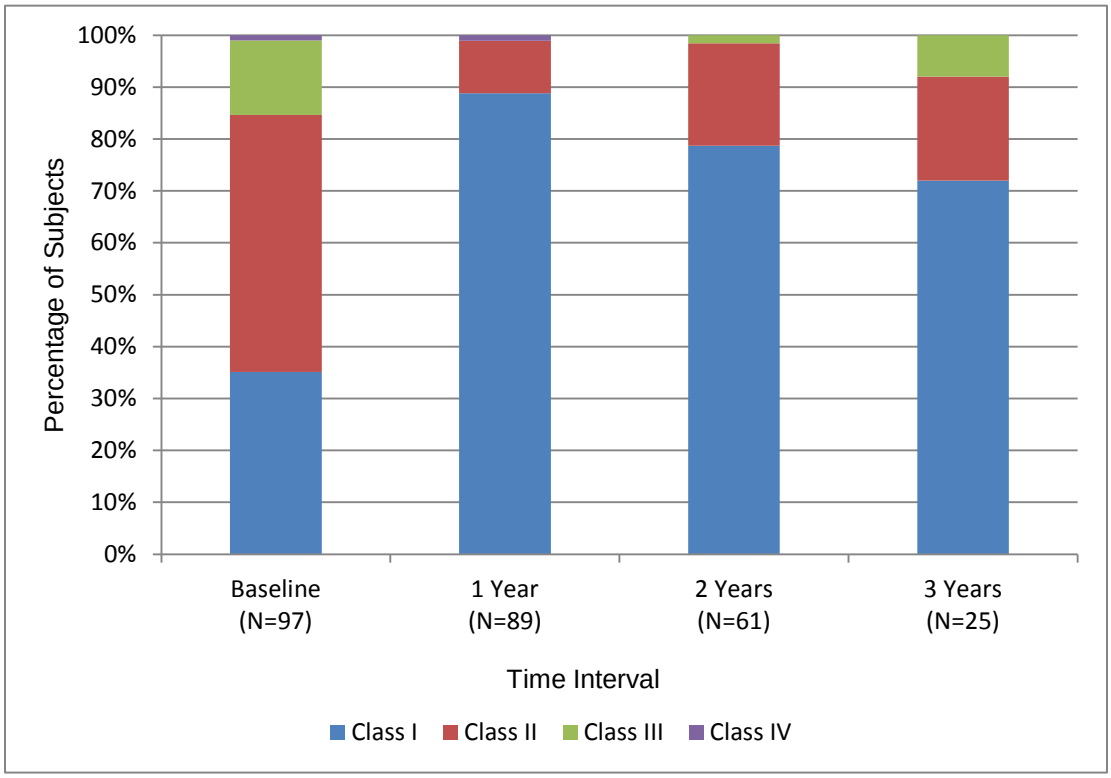

Figure 14: New York Heart Association Classification – Implanted >24 hours Cohort (N = 99)

10.3 Pooling of Long-Term Follow-Up PAS and New Enrollment PAS Studies

A post hoc analysis was performed on the pooled data from the Long-term Follow-up PAS and New Enrollment PAS, reporting 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 was identified as the primary effectiveness outcome measure.

10.3.1 Pooled Subject Demographics

Table 22 presents the subject demographics and baseline characteristics of the enrolled subjects in the pooled dataset. The baseline demographics were generally similar in the two studies (Table 3 and Table 11), with the exceptions that bioprosthetic valve targets and a mixed indication (stenosis and regurgitation) were proportionately more frequent in the New Enrollment PAS.

Table 22: 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[1]	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]

Assessment	Enrolled Cohort (N = 302)
Primary Indication	
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)
Moderate	32.4% (95/293)
Severe	45.4% (133/293)
Mean RVOT Gradient by Site Echo (mm Hg)[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.

10.3.2 Pooled Safety Results

10.3.2.1 Acute Procedure-related Serious Adverse Events

Table 23 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 23: 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)

10.3.2.2 Device-related Adverse Events

Table 24 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 24: Summary of Pooled Device-related Adverse Events Through 1 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)

10.3.3 Pooled Safety and Effectiveness Outcome Measures

Table 25 provides the results of the safety and effectiveness outcome measures utilizing the Generalized Estimating Equation (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 25: Pooled Rates for Safety and Effectiveness Outcome Measures 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)
Reintervention	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 interval is provided to illustrate the variability only and should not be used to draw any statistical conclusion.

11.0 Disclaimer of Warranty

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M054316T001 Rev. 1A

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