Medtronic

Melody™ Transcatheter Pulmonary Valve
Ensemble™ Transcatheter Valve Delivery System
Ensemble™ II 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
	For US Audiences Only

1.0 Device description

The implant system consists of the Melody™ transcatheter pulmonary valve, model PB10 (stented bovine jugular vein valve) and either the Ensemble™ transcatheter valve delivery system, model NU10 or the Ensemble™ II transcatheter valve delivery system, model ENS10.

1.1 Melody™ transcatheter pulmonary valve (TPV)

The TPV consists of a heterologous (bovine) jugular vein valve sutured within a laser-welded, platinum-iridium stent with gold brazing of the welds. The TPV is available in a 16 mm bovine jugular vein (nominal length of 30 mm) and an 18 mm bovine jugular vein (nominal length of 28 mm). A final sterilization step is performed using a sterilant that contains 1% glutaraldehyde and 20% isopropyl alcohol, and in which the TPV is preserved and packaged until used. Adequate rinsing with isotonic saline solution must be performed before implantation to reduce the glutaraldehyde concentration.

See Table 1 for TPV sizing recommendations.

Table 1: TPV sizing

TPV catalog number	Diameter of intended implant location	Maximum expanded inner diameter of the TPV
PB1016	18 mm to 20 mm	20 mm
PB1018	18 mm to 22 mm	22 mm

1.2 Ensemble™ and Ensemble™ II transcatheter valve delivery system (delivery system)

Each delivery system consists of a balloon-in-balloon catheter with a retractable polytetrafluoroethylene (PTFE) sheath large enough to cover the TPV 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'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 delivery system 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. The Ensemble™ II delivery system also includes radiopaque marker bands on the delivery system beneath the balloons. The marker bands are intended to aid in visibility of balloon location under fluoroscopy.

See Table 2 for delivery system sizes.

Table 2: Delivery system sizes

Ensemble™ delivery system catalog number	Ensemble™ II delivery system catalog number	Outer balloon outer diameter
NU1018	ENS1018	18 mm
NU1020	ENS1020	20 mm
NU1022	ENS1022	22 mm

2.0 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 right ventricular outflow tract (RVOT) conduit or surgical bioprosthetic pulmonary valve that has ≥ moderate regurgitation, and/or a mean RVOT gradient ≥35 mm Hg.

3.0 Contraindications

None known.

4.0 Warnings and precautions

4.1 Warnings

Do not implant in the aortic or mitral position. Preclinical bench testing of the 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.

4.1.1 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 implant location. If aortography demonstrates a coronary artery branch passing beneath or otherwise close to the implant location, or if coronary anatomy could not be determined, further evaluation with selective coronary arteriography and simultaneous inflation of an angioplasty balloon across the implant location obstruction should be performed. If inflation of the balloon demonstrates any suggestion of coronary compression, as demonstrated by simultaneous selective coronary arteriography, the patient should be deemed anatomically unsuitable for TPV implantation.

The risk of conduit rupture should be considered in all patients undergoing TPV implantation in a conduit. 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.

4.1.2 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).

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 TPV 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 TPV 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 TPV 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 as shown in Table 1, as this may result in a regurgitant TPV.

4.1.3 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 delivery system at any time during the procedure.

4.1.4 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 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 delivery system 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 delivery system depends on its integrity. Use caution when handling the delivery system. Damage may result from kinking, stretching, or forceful wiping of the delivery system.
- This delivery system 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 TPV on the balloon, the orientation should be verified.

  Note: The blue suture should be adjacent to the blue tip of the delivery system.
- Do not remove the tag attached to the TPV until the TPV 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 TPV and helps with proper orientation of the TPV on the delivery system.
- The inflation diameter of the balloon used during TPV 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 valve must be known at all times. No change of orientation should occur as the TPV 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 TPV.
- 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 delivery system back into the sheath.
- If resistance is felt upon attempted removal of the 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 TPV, and a second guidewire placed in the pulmonary artery. The original delivery system and guidewire can then be carefully removed together under fluoroscopic guidance.
- The safety and effectiveness of a Melody™ TPV implanted within a failed preexisting transcatheter bioprosthesis or within another Melody™ TPV have not been demonstrated.

5.0 Potential adverse events

The following list includes potential procedural complications that may result from implantation of the TPV:

- 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

The following list includes potential device-related adverse events that may occur following TPV implantation:

- 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.

6.2.1 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.

6.2.2 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™ clinical studies 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 3.0 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 3.0 T MRI System. The lumen of the device was obscured.

For deployment of a Melody™ TPV inside a bioprosthesis, consult the MRI labeling pertaining to the bioprosthesis for additional image artifact information. It may be necessary to optimize MR imaging parameters for the presence of this implant.

Scanning under the conditions defined above may be performed immediately after implantation.

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 delivery system is sterilized with ethylene oxide gas and packaged in a double pouch. The delivery system is sterile if the pouches are undamaged and unopened. Do not use the delivery system if the outer pouch is damaged. The delivery system should never be stored in only the inner pouch. The inner pouch does not provide a sterile barrier. 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 delivery system at room temperature and away from direct sunlight. The delivery system should never be stored in only the inner pouch. The inner pouch does not provide a sterile barrier.

Appropriate inventory control should be maintained so that devices with the earliest Use By dates are preferentially used to avoid expiration. Devices must be used by the Use By date shown on the product labels.

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 are 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 it 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 TPV 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 TPV 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.

   If assessing a bioprosthesis, adjust the fluoroscopy angles so the bioprosthesis annulus and/or commissures are in one plane or in profile. Consider the features of the bioprosthesis when determining the optimal placement for the TPV.
6. To assess for suitability of TPV implantation, follow either step a (for conduits) or step b (for bioprosthetic valves).

   a. **For conduits:** 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. 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.

   b. **For bioprosthetic valves:** Obtain angiographic measurements of the intended implantation site to assess suitability for TPV implantation. If angiographic measurements are unclear or if there is a question of the inner diameter (ID) of the bioprosthesis being too large for implant (>22 mm), a low-pressure sizing balloon (<811 kPa [<8 atm]) may be used to further assess the ID. If the current ID of the bioprosthesis is <22 mm and is ≥2 mm less than the manufacturer's published ID, use a balloon to predilate the bioprosthesis. The balloon should not exceed the manufacturer's published ID of the bioprosthesis. If the bioprosthesis ID measures >22 mm, the bioprosthesis should be considered too large for Melody™ TPV implantation.

Note: If obstruction is noted, further preparation of the implantation site (for example, predilation) may be required to facilitate optimal relief of obstruction before implanting the TPV.

7. Perform final sizing using a balloon diameter that clearly demonstrates the narrowest portion of the conduit or bioprosthesis (at a pressure of <811 kPa [<8 atm]). If the coronary arteries are an acceptable distance from the implant site, the anatomy is considered suitable for Melody™ TPV implantation. See Table 1 for sizing recommendations.

   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 patient 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

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 tag 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 end) 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 onto the delivery system.
2. Remove the serial number tag by cutting the suture, which attaches the tag to the TPV.

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 Table 1. 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 or bioprosthetic valve diameter.

2. Flush the delivery system guidewire lumen and the side port. Prepare the balloons by completely deflating with a 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 TPV 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 TPV over the tip of the delivery system and center over the balloons.
4. Verify that the outflow end of the TPV is oriented toward the distal end of the delivery system. The outflow end of the TPV can be detected by the blue suture used to attach the valve at this location.
5. Gently crimp the TPV onto the balloon using finger pressure and a rolling action to exert equal pressure on all sides of the TPV to elongate the stent. Crimp only until no movement is felt on the delivery system.

   Avoid bending or twisting the TPV.

   Ensure the blue suture is adjacent to the blue tip of the delivery system to ensure proper orientation of the TPV for delivery.
6. Carefully slide the sheath over the TPV and balloons, ensuring that the crowns at the inflow end of the TPV do not get caught on the sheath as it is advanced over the TPV. 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.

   Note: Check to ensure that the blue suture is adjacent to the blue tip of the delivery system.
7. 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 it 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 TPV is intended to be deployed. This requires manipulations of the delivery system and the guidewire. **Maintain adequate guidewire position at all times.**
8. 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 delivery system shaft. While uncovering, ensure that there is no inadvertent movement of the TPV, which could possibly lead to the loss of the appropriate TPV position.
9. 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 TPV and full retraction of the sheath. Further minor adjustments of the position of the TPV are still possible at this point.
10. 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.
11. Measure the RV-PA pressure. If a significant gradient exists, perform balloon dilation with a high-pressure balloon in order to minimize the gradient.
12. Compare the RV pressure with the systemic pressure measured through the arterial approach.

13. Perform a contrast injection into the proximal main PA (or distal RVOT) to demonstrate valve function and position. Ensure that the valve is not held open by the guidewire and the delivery system as this would give the false impression of pulmonary regurgitation.

14. Remove the catheters, guidewires, and sheaths while maintaining hemostasis.

    Note: The delivery system is for single use and should only be inflated once. Do not use the delivery system to expand the TPV after initial implantation. The TPV may be expanded after placement by using a different balloon catheter. To minimize the risk of creating regurgitation, do not exceed the maximum recommended size as shown in Table 1.

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

Table 3: Melody™ TPV sizing chart

Delivery system size – inner balloon / outer balloon	Inner balloon maximum applied pressure (RBP)		Outer balloon applied pressure		Corresponding TPV 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 4: Approximate length of the TPV following deployment with the corresponding delivery system

Expanded outer balloon outer diameter (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 TPVs

Medtronic is interested in obtaining recovered explanted TPVs. Specific pathological studies of the explanted TPV 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 TPV 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 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 premarket investigational device exemption (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 humanitarian device exemption (HDE) approval in 2010. All subjects had imaging data through 1 year analyzed by the imaging core laboratory. A cardiopulmonary exercise testing (CPET) core laboratory was utilized for review and interpretation of CPET exams through 5 years. The Long-term Follow-up PAS study continues to use an independent pathology core laboratory to analyze explanted devices.

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 June 2016. 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 73.0 ± 20.6 months.

10.1.1 Subject demographics

Table 5 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 5: Long-term Follow-up PAS: subject demographics/baseline data – enrolled cohort (N = 171)

Assessment	Enrolled cohort (N = 171)
Gender	
Female	37.4% (64/171)
Male	62.6% (107/171)
Age (years)	
n	171
Mean ± SD	21.8 ± 9.8
Median [min, max]	19.0 [7.0, 53.0]
Original diagnosis	
Aortic valve disease (Ross)	20.5% (35/171)
Double outlet right ventricle	4.7% (8/171)
Isolated pulmonary stenosis	1.8% (3/171)
Pulmonary atresia	0.6% (1/171)
Tetralogy of Fallot	50.3% (86/171)
Transposition of the great arteries	10.5% (18/171)
Truncus arteriosus	10.5% (18/171)
Other[1]	1.2% (2/171)
RVOT conduit type	
Homograft	73.7% (126/171)
Biological valved conduit	15.8% (27/171)
Bioprosthesis	4.7% (8/171)
Synthetic	5.8% (10/171)
Other	0.0% (0/171)
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 diagnoses included: 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 is provided in Table 6. 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 6: Long-term Follow-up PAS: procedural data – catheterized cohort (N = 167)

Assessment	Catheterized cohort (N = 167)
Anesthesia	
Local	0.0% (0/167)
General	100.0% (167/167)
Venous site access	
Femoral vein	94.6% (158/167)
Internal 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 ± 65.5
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-right pulmonary artery (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 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 7: 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 8 presents the incidence of device-related adverse events and freedom from event at 1 year, 3 years, 5 years, and 7 years postimplant.

Table 8: Long-term Follow-up PAS: summary of device-related adverse events during follow-up – implanted cohort (N = 150)

Event[1, 2]	Subjects with event (N = 150)	Freedom from event at 1 year (95% CI)	Freedom from event at 3 years (95% CI)	Freedom from event at 5 years (95% CI)	Freedom from event at 7 years (95% CI)
Stent fracture (all)	34.0% (51/150)	82.4% (75.2%, 87.6%)	73.5% (65.6%, 79.9%)	66.0% (57.2%, 73.5%)	64.0% (54.4%, 72.1%)
Valve dysfunction: stenosis (all)	19.3% (29/150)	94.6% (89.5%, 97.2%)	85.6% (78.8%, 90.4%)	81.2% (73.5%, 86.9%)	79.3% (70.8%, 85.7%)
Stent fracture: major	15.3% (23/150)	97.3% (92.9%, 99.0%)	88.3% (81.7%, 92.6%)	85.4% (78.2%, 90.3%)	83.6% (75.7%, 89.2%)
with fragment embolization	1.3% (2/150)	--	--	--	
Prosthetic valve endocarditis	8.7% (13/150)	97.9% (93.8%, 99.3%)	97.3% (92.9%, 99.0%)	95.7% (90.5%, 98.1%)	89.2% (79.7%, 94.4%)
Tricuspid regurgitation	8.7% (13/150)	99.3% (95.4%, 99.9%)	96.6% (92.0%, 98.6%)	92.9% (87.0%, 96.1%)	91.1% (84.4%, 95.0%)
Paravalvular leak: minor	2.0% (3/150)	99.3% (95.4%, 99.9%)	99.3% (95.4%, 99.9%)	99.3% (95.4%, 99.9%)	99.3% (95.4%, 99.9%)
Valve dysfunction: regurgitation	1.3% (2/150)	100.0% (NA)	100.0% (NA)	99.3% (95.4%, 99.9%)	99.3% (95.4%, 99.9%)
Pulmonary thromboembolism	0.7% (1/150)	100.0% (NA)	99.3% (95.4%, 99.9%)	99.3% (95.4%, 99.9%)	99.3% (95.4%, 99.9%)
Embolization of the TPV	0.0% (0/150)	100.0% (NA)	100.0% (NA)	100.0% (NA)	100.0% (NA)
Hemorrhage	0.0% (0/150)	100.0% (NA)	100.0% (NA)	100.0% (NA)	100.0% (NA)
Nonstructural dysfunction	0.0% (0/150)	100.0% (NA)	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)	100.0% (NA)
Structural deterioration of the TPV	0.0% (0/150)	100.0% (NA)	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)	100.0% (NA)
Valve dysfunction: mixed	0.0% (0/150)	100.0% (NA)	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 9), 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 9: 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)	18.5% (10/54)
Stent fracture: major with fragment embolization	20.8% (20/96) 2.1% (2/96)	5.6% (3/54) 0.0% (0/54)
Valve dysfunction: stenosis (all)	22.9% (22/96)	13.0% (7/54)
Valve dysfunction: regurgitation	2.1% (2/96)	0.0% (0/54)
Valve dysfunction: mixed	0.0% (0/96)	0.0% (0/54)
Valvular regurgitation, tricuspid	11.5% (11/96)	3.7% (2/54)
Prosthetic valve endocarditis	10.4% (10/96)	5.6% (3/54)
Pulmonary thromboembolism	1.0% (1/96)	0.0% (0/54)
Paravalvular leak: minor	3.1% (3/96)	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 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 7 years postimplant was estimated to be 83.6%.

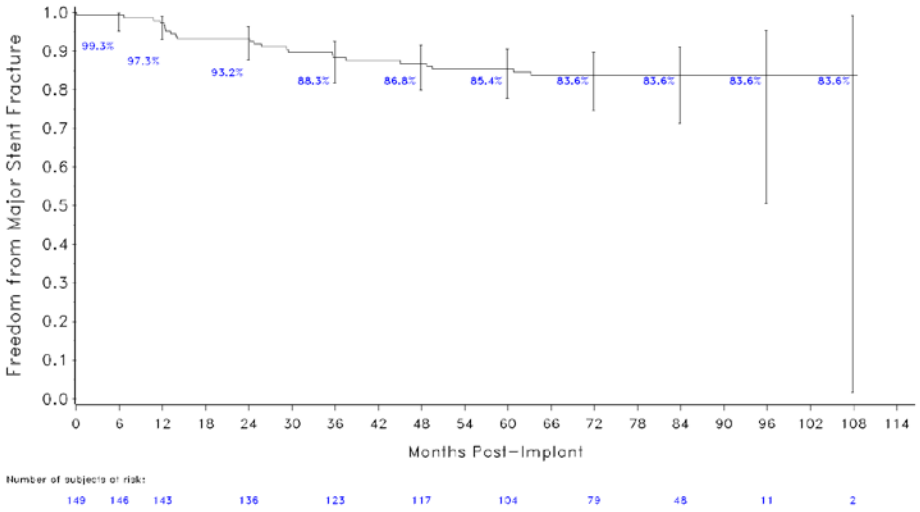

Figure 1: Kaplan-Meier freedom from major stent fracture – implanted >24 hours cohort (N = 149)

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, 60 = 1825 to 2189 days, 72 = 2190 to 2554 days, 84 = 2555 to 2919 days, 96 = 2920 to 3284 days, and 108 = 3285 to 3649 days.
2. The cumulative probability of event-free estimate is based on the Kaplan-Meier (KM) method.
3. 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 7 years postimplant was estimated to be 89.2%.

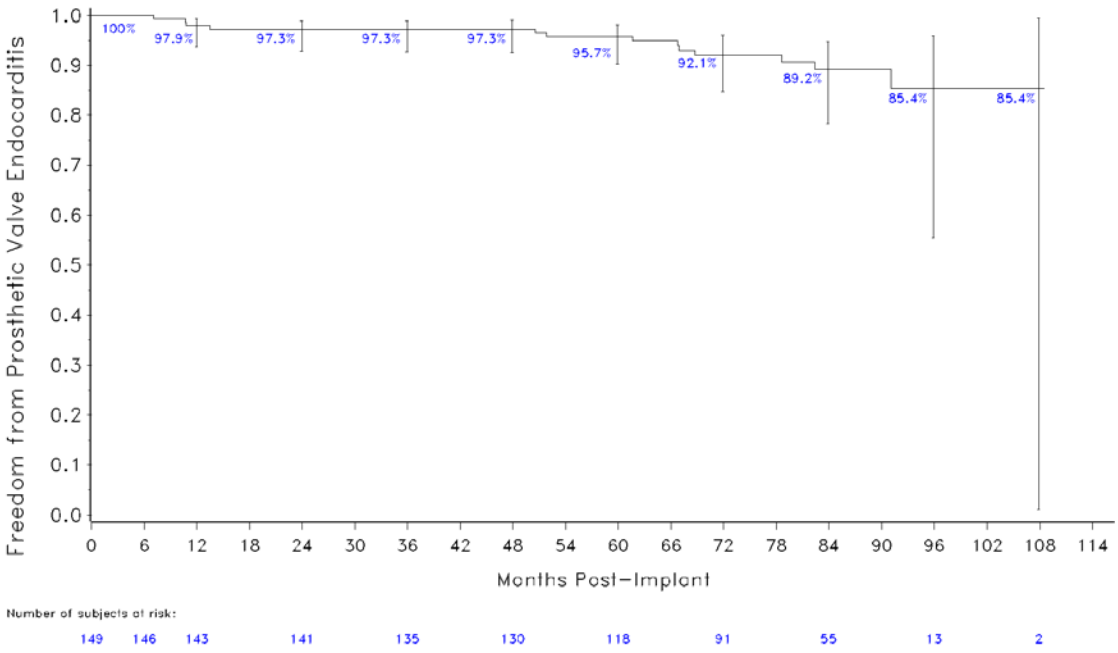

Figure 2: Kaplan-Meier freedom from prosthetic valve endocarditis – implanted >24 hours cohort (N = 149)

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, 60 = 1825 to 2189 days, 72 = 2190 to 2554 days, 84 = 2555 to 2919 days, 96 = 2920 to 3284 days, and 108 = 3285 to 3649 days.
2. The cumulative probability of event-free estimate is based on the KM method.
3. 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 7 years postimplant was estimated to be 93.2%.

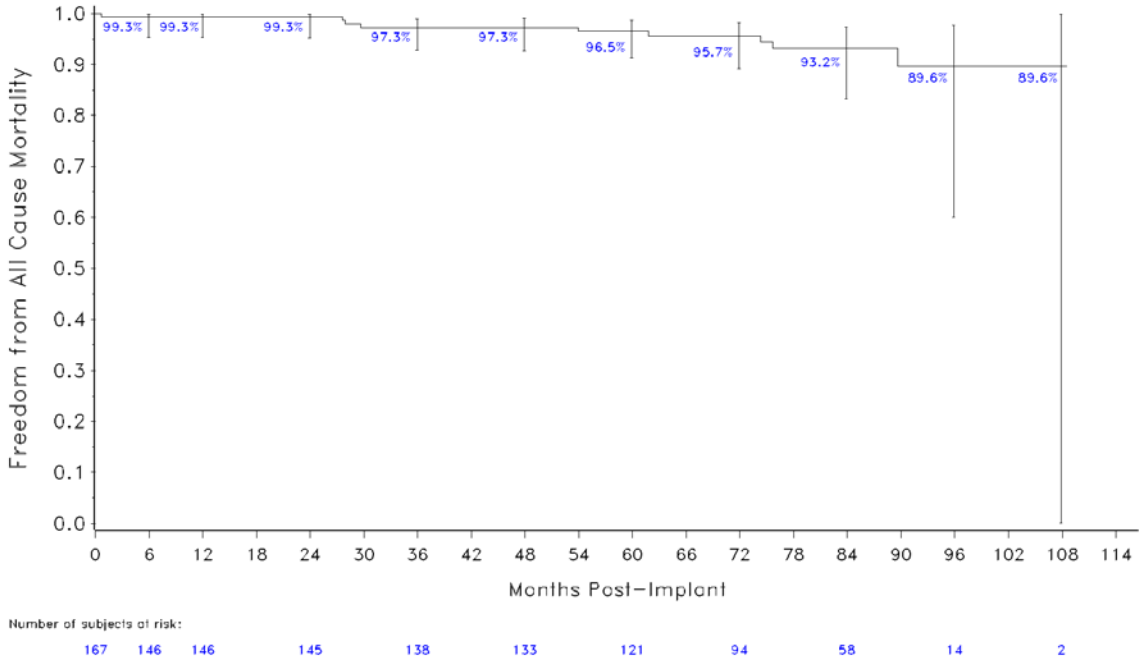

Figure 3: Kaplan-Meier freedom from all-cause mortality – catheterized cohort (N = 167)

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, 60 = 1825 to 2189 days, 72 = 2190 to 2554 days, 84 = 2555 to 2919 days, 96 = 2920 to 3284 days, and 108 = 3285 to 3649 days.
2. The cumulative probability of event-free estimate is based on the KM method.
3. 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 with a Melody™ TPV implant 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 13. 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 6 subjects had mild or greater PR by angiography.

Table 10: Long-term Follow-up PAS: procedural success – attempted implant cohort (N = 150)

	Implanted cohort (N = 150)
Procedural success	94.7% (142/150)
Procedural failure	5.3% (8/150)
Melody™ TPV not fixated within the desired location	0.0% (0/150)
RV-PA peak-to-peak gradient (measured in the catheterization lab) at least 35 mm Hg postimplant	0.7% (1/150)
More than trivial pulmonary regurgitation by angiography postimplant[1]	4.0% (6/149)
Explant of the Melody™ TPV within 24 hours postimplant	0.7% (1/150)

[1] Postimplant pulmonary regurgitation was not assessed in the explanted subject.

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 7 years, the freedom from TPV dysfunction was estimated to be 63.5%.

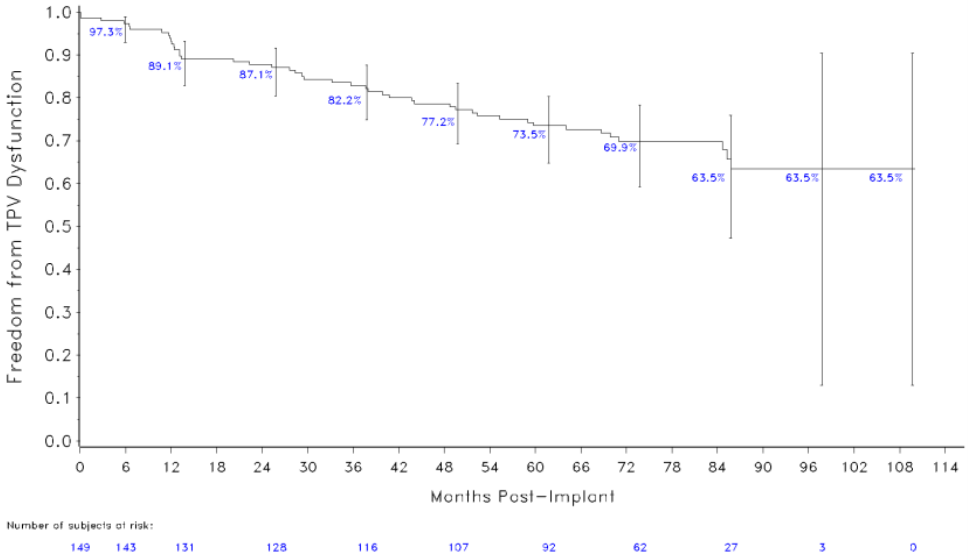

Figure 4: Kaplan-Meier freedom from TPV dysfunction – implanted >24 hours cohort (N = 149)

Notes:

1. 0 = 0 to 182 days, 6 = 183 to 419 days, 12 = 420 to 785 days, 24 = 786 to 1150 days, 36 = 1151 to 1515 days, 48 = 1516 to 1880 days, 60 = 1881 to 2245 days, 72 = 2246 to 2610 days, 84 = 2611 to 2975 days, 96 = 2976 to 3340 days, and 108 = 3341 to 3705 days.
2. The cumulative probability of event-free estimate is based on the KM method.
3. 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.

10.1.4.3 Freedom from RVOT conduit reoperation

At 7 years postimplant, the freedom from RVOT conduit reoperation was estimated to be 88.8%.

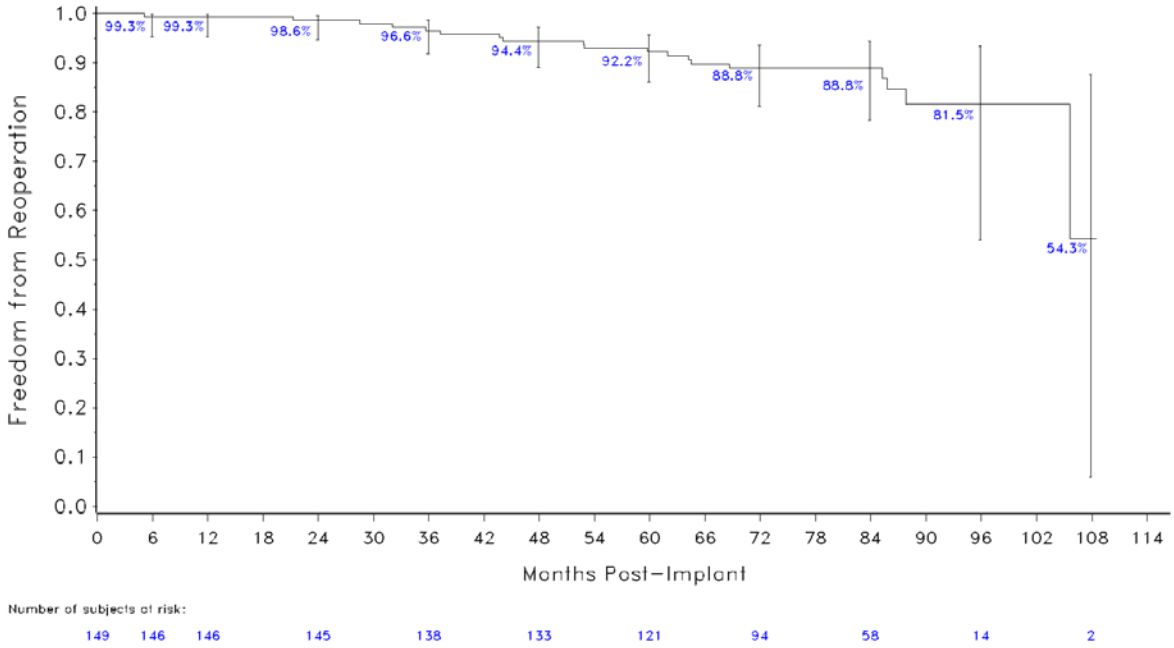

Figure 5: Kaplan-Meier freedom from RVOT conduit reoperation – implanted >24 hours cohort (N = 149)

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, 60 = 1825 to 2189 days, 72 = 2190 to 2554 days, 84 = 2555 to 2919 days, 96 = 2920 to 3284 days, and 108 = 3285 to 3649 days
2. The cumulative probability of event-free estimate is based on the KM method.
3. 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 7 years postimplant was estimated to be 78.9%.

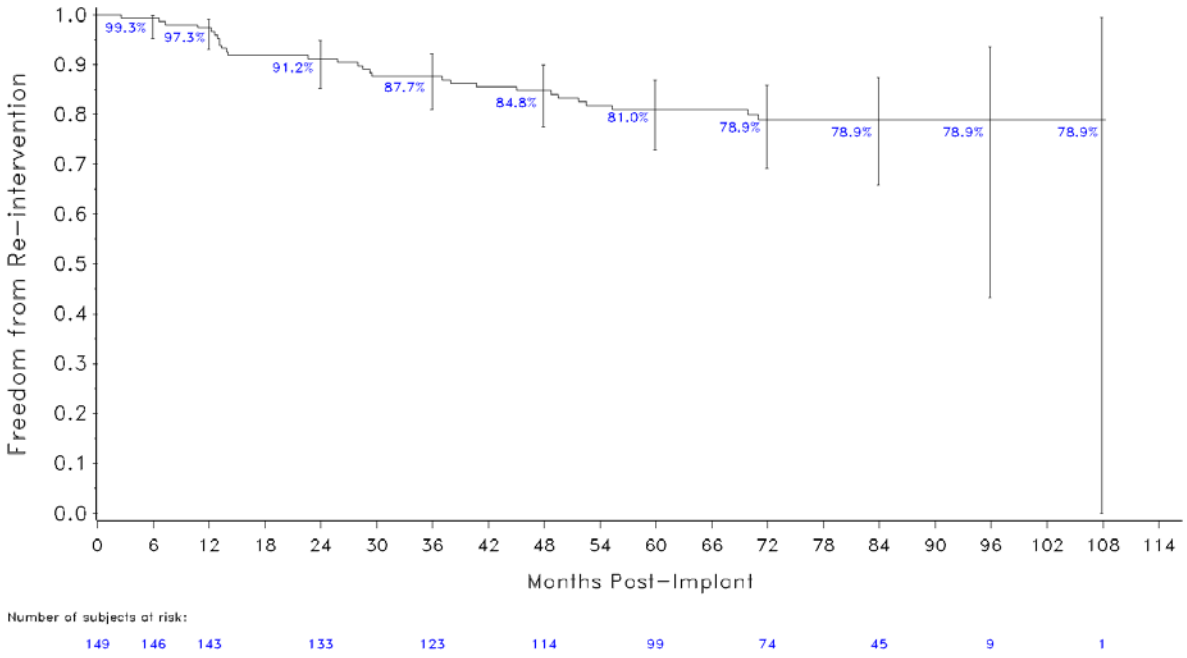

Figure 6: Kaplan-Meier freedom from catheter reintervention on the TPV – implanted >24 hours cohort (N = 149)

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, 60 = 1825 to 2189 days, 72 = 2190 to 2554 days, 84 = 2555 to 2919 days, 96 = 2920 to 3284 days, and 108 = 3285 to 3649 days.
2. The cumulative probability of event-free estimate is based on the KM method.
3. 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 9 years of follow-up, the vast majority of subjects had no more than mild PR.

Table 11: Long-term Follow-up PAS: pulmonary regurgitation by time interval – implanted >24 hours cohort (N = 149)

Degree of regurgitation[1, 2]	None	Trace	Mild	Moderate	Severe
Preimplant (n = 149)	5.5% (8/146)	3.4% (5/146)	12.3% (18/146)	30.8% (45/146)	47.9% (70/146)
Discharge (n = 148)	71.7% (104/145)	24.8% (36/145)	3.4% (5/145)	0.0% (0/145)	0.0% (0/145)
3 months (n = 146)	75.5% (108/143)	19.6% (28/143)	4.9% (7/143)	0.0% (0/143)	0.0% (0/143)
6 months (n = 143)	76.3% (106/139)	20.9% (29/139)	2.9% (4/139)	0.0% (0/139)	0.0% (0/139)
1 year (n = 142)	79.1% (110/139)	14.4% (20/139)	5.8% (8/139)	0.7% (1/139)	0.0% (0/139)
2 years (n = 137)	70.7% (94/133)	22.6% (30/133)	6.8% (9/133)	0.0% (0/133)	0.0% (0/133)
3 years (n = 120)	69.6% (78/112)	23.2% (26/112)	7.1% (8/112)	0.0% (0/112)	0.0% (0/112)
4 years (n = 110)	72.3% (73/101)	20.8% (21/101)	5.9% (6/101)	1.0% (1/101)	0.0% (0/101)
5 years (n = 100)	64.1% (59/92)	25.0% (23/92)	10.9% (10/92)	0.0% (0/92)	0.0% (0/92)
6 years (n = 80)	50.7% (38/75)	29.3% (22/75)	20.0% (15/75)	0.0% (0/75)	0.0% (0/75)
7 years (n = 57)	55.8% (29/52)	26.9% (14/52)	15.4% (8/52)	1.9% (1/52)	0.0% (0/52)
8 years (n = 20)	31.6% (6/19)	52.6% (10/19)	15.8% (3/19)	0.0% (0/19)	0.0% (0/19)
9 years (n = 2)	50.0% (1/2)	50.0% (1/2)	0.0% (0/2)	0.0% (0/2)	0.0% (0/2)

[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, 3 subjects at 3 years, 9 subjects at 4 years, 8 subjects at 5 years, 5 subjects at 6 years, 5 subjects at 7 years, and 1 subject at 8 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 12.

Table 12: Long-term Follow-up PAS: RVOT mean gradient by time interval – implanted >24 hours cohort (N = 149)

RVOT mean gradient (mm Hg)[1]	n[2]	Mean ± SD	Median [min, max]	Q1, Q3
Preimplant (n = 149)	147	32.1 ± 13.9	32.0 [5.2, 97.0]	21.0, 40.8
Discharge (n = 148)	147	17.7 ± 7.7	17.0 [3.4, 51.0]	12.0, 22.0
3 months (n = 146)	145	17.5 ± 7.9	17.0 [4.0, 53.0]	13.0, 20.0
6 months (n = 143)	142	17.6 ± 7.6	16.0 [5.0, 48.0]	12.6, 21.0
1 year (n = 142)	140	18.7 ± 9.1	17.0 [4.0, 51.0]	12.0, 23.0
2 years (n = 137)	136	17.6 ± 10.0	15.5 [4.0, 72.0]	11.0, 22.0
3 years (n = 120)	117	17.6 ± 7.9	16.0 [4.0, 41.1]	12.0, 22.0
4 years (n = 110)	104	18.3 ± 8.7	16.5 [4.0, 47.0]	12.0, 24.0
5 years (n = 100)	95	17.5 ± 8.4	16.0 [4.2, 55.0]	12.0, 21.0
6 years (n = 80)	77	18.2 ± 8.3	18.0 [2.1, 43.0]	13.0, 23.0
7 years (n = 57)	54	17.9 ± 9.8	16.0 [4.0, 55.0]	11.8, 20.0
8 years (n = 20)	19	20.6 ± 8.5	18.0 [8.0, 40.0]	14.0, 26.0
9 years (n = 2)	2	15.5 ± 7.8	15.5 [10.0, 21.0]	10.0, 21.0

[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, 6 subjects at 4 years, 5 subjects at 5 years, 3 subjects at 6 years, 3 subjects at 7 years, and 1 subject at 8 years postimplant.

10.1.4.6 NYHA

Table 13 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.

Table 103: Long-term Follow-up PAS: NYHA functional class by time interval – implanted >24 hours cohort (N = 149)

NYHA classification[1]	I	II	III	IV
Baseline (N = 149)	14.1% (21/149)	69.1% (103/149)	16.1% (24/149)	0.7% (1/149)
1 year (N = 141)	76.4% (107/140)	22.9% (32/140)	0.7% (1/140)	0.0% (0/140)
2 years (N = 137)	75.4% (101/134)	24.6% (33/134)	0.0% (0/134)	0.0% (0/134)
3 years (N = 121)	78.0% (92/118)	20.3% (24/118)	0.8% (1/118)	0.8% (1/118)
4 years (N = 110)	80.6% (87/108)	19.4% (21/108)	0.0% (0/108)	0.0% (0/108)
5 years (N = 101)	85.9% (85/99)	13.1% (13/99)	0.0% (0/99)	1.0% (1/99)
6 years (N = 82)	84.9% (62/73)	15.1% (11/73)	0.0% (0/73)	0.0% (0/73)
7 years (N = 58)	85.2% (46/54)	14.8% (8/54)	0.0% (0/54)	0.0% (0/54)
8 years (N = 21)	90.0% (18/20)	10.0% (2/20)	0.0% (0/20)	0.0% (0/20)
9 years (N = 2)	100.0% (2/2)	0.0% (0/2)	0.0% (0/2)	0.0% (0/2)

[1] NYHA was unable to be assessed for 1 subject at 1 year, 3 subjects at 2 years, 3 subjects at 3 years, 2 subjects at 4 years, 2 subjects at 5 years, 9 subjects at 6 years, 4 subjects at 7 years, and 1 subject at 8 years postimplant.

10.1.5 Primary outcome measures

The primary objective of the Long-term Follow-up PAS is to confirm the long-term functionality of implantation of the Medtronic Melody™ TPV at 5 years is no worse than the historical control established through literature review.

The primary endpoint is TPV dysfunction, which is a composite outcome defined as:

- Reoperation for conduit dysfunction or device-related reasons
- Catheter reintervention on the TPV
- Hemodynamic dysfunction of the TPV
    - Moderate or greater pulmonary regurgitation, and/or
    - Mean RVOT gradient greater than 40 mm Hg

10.1.5.1 Primary Hypothesis

This study was designed to test the null hypothesis that the true freedom from TPV dysfunction at 5 years after Melody™ TPV implantation (PMelody) is less than or equal to 36% (PControl). To reject the null hypothesis means that freedom from TPV dysfunction at 5 years after Melody™ TPV implantation (PMelody) is greater than 36% (PControl). The null (H0) and alternative (HA) hypotheses are written as follows:

H0: PMelody ≤ PControl

HA: PMelody > PControl

Analysis was performed to determine if the freedom from TPV dysfunction at 5 years is significantly greater than the historical control rate of 36%. The freedom from TPV dysfunction will be described by Kaplan-Meier statistics. Peto's method for the standard error estimate was used. A p-value less than 0.05 was considered statistically significant.

The primary objective was met with 73.5% (p-value < 0.0001) of subjects free from TPV dysfunction at 5 years after the Melody™ TPV implant.

Table 14: Subjects with TPV dysfunction at 5 years postoperative – implanted >24 hours cohort (N = 149)

Number of subjects in the analysis	KM rate of freedom from TPV dysfunction	Peto standard error	One-sided 95% lower confidence bound for KM rate	Hypothesis testing	
149	73.5%	4.0%	66.4%	p-value	Objective met
				<0.0001	yes

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 5 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 June 2016. 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 45.0 ± 14.0 months.

10.2.1 Subject demographics

Table 15 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 (39.7%) followed by aortic valve disease in subjects having undergone a Ross procedure (17.6%). Homografts were the most common target for Melody™ TPV implantation.

Table 15: New Enrollment PAS: subject demographics/baseline data – enrolled cohort (N = 131)

Assessment	Enrolled cohort (N = 131)
Gender	
Female	33.6% (44/131)
Male	66.4% (87/131)
Age (years)	
n	131
Mean ± SD	20.1 ± 9.8
Median [min, max]	17.0 [5.0, 50.0]
Original diagnosis	
Aortic valve disease (Ross)	17.6% (23/131)
Double outlet right ventricle	7.6% (10/131)
Isolated pulmonary stenosis	3.8% (5/131)
Pulmonary atresia	3.1% (4/131)
Tetralogy of Fallot	39.7% (52/131)
Transposition of the great arteries	7.6% (10/131)
Truncus arteriosus	15.3% (20/131)
Other[1]	5.3% (7/131)
RVOT conduit type	
Homograft	67.2% (88/131)
Biological valved conduit	17.6% (23/131)
Bioprosthesis	13.7% (18/131)
Synthetic	1.5% (2/131)
Other	0.0% (0/131)
RVOT conduit size (mm) when originally implanted	
n	112
Mean ± SD	21.0 ± 3.2
Median [min, max]	21.0 [15.0, 30.0]
Bioprosthesis size (mm) when originally implanted	
n	18
Mean ± SD	24.6 ± 2.8
Median [min, max]	25.0 [19.0, 31.0]

[1] Other original diagnoses included: situs ambiguus asplenia, dextrocardia, and AV canal (n = 1); 22q11 deletion, mesocardia, posterior malalignment VSD w/coarctation of the aorta (n = 1); CHARGE association (AVSD, pulmonary atresia) (n = 1); interrupted aortic arch (IAA), ASD, VSD, subaortic stenosis (n = 1); pulmonary stenosis with VSD (n = 1); IAA and VSD (n=1); pulmonary stenosis, sinus venosus ASD, interrupted inferior vena cava, sick sinus syndrome, VSD (n = 1).

10.2.2 Procedural data

A summary of procedural data is provided in Table 16. 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 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 16: New Enrollment PAS: procedural data – catheterized cohort (N = 120)

Assessment[1]	Catheterized cohort (N = 120)
Venous site access	
Femoral vein	88.3% (106/120)
Internal 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: conduit angioplasty (n = 4); existing PA stent redilation (n = 3); pulmonary valvuloplasty (n = 1); existing RVOT stent redilation (n = 1); left ventricular assist device (LVAD) placed (n = 1).

10.2.3 Safety results

10.2.3.1 Acute procedure-related serious adverse events

Of the 120 subjects catheterized, 11 (9.2%) experienced acute (day of catheterization) serious adverse events classified as either possibly or definitely related to the procedure. Six 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 (9.2%) 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 (5.0% versus 1.8%).

Table 17: New Enrollment PAS: summary of acute procedure-related serious adverse events – catheterized cohort (N = 120)

Procedure-related serious adverse event	Catheterized cohort (N = 120)
Subjects with procedure-related SAEs	9.2% (11/120)
RVOT conduit rupture or dissection	5.0% (6/120)
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 18 presents the incidence of device-related adverse events and freedom from event at 1 year, 3 years, and 5 years postimplant.

Table 18: New Enrollment PAS: summary of device-related adverse events during follow-up – implanted cohort (N = 100)

Event[1,2]	Subjects with event (n = 100)	Freedom from event at 1 year (95% CI)	Freedom from event at 3 years (95% CI)	Freedom from event at 5 years (95% CI)
Stent fracture (all)	15.0% (15/100)	90.8% (83.0%, 95.1%)	84.2% (74.9%, 90.3%)	84.2% (74.9%, 90.3%)
Prosthetic valve endocarditis	13.0% (13/100)	97.0% (90.9%, 99.0%)	89.4% (81.1%, 94.2%)	84.9% (73.9%, 91.5%)
Valve dysfunction: stenosis (all)	12.0% (12/100)	99.0% (93.2%, 99.9%)	90.2% (81.9%, 94.8%)	86.1% (76.1%, 92.1%)
Valve dysfunction: regurgitation	7.0% (7/100)	98.0% (92.3%, 99.5%)	96.8% (90.7%, 98.9%)	88.7% (75.8%, 94.9%)
Stent fracture: major	6.0% (6/100)	99.0% (93.2%, 99.9%)	95.6% (88.6%, 98.4%)	91.0% (81.3%, 95.8%)
with fragment embolization	1.0% (1/100)	--	--	--
Paravalvular leak: major	1.0% (1/100)	99.0% (93.2%, 99.9%)	99.0% (93.2%, 99.9%)	99.0% (93.2%, 99.9%)
Paravalvular leak: minor	1.0% (1/100)	99.0% (93.2%, 99.9%)	99.0% (93.2%, 99.9%)	99.0% (93.2%, 99.9%)
Pulmonary thromboembolism	1.0% (1/100)	99.0% (93.2%, 99.9%)	99.0% (93.2%, 99.9%)	99.0% (93.2%, 99.9%)
Structural deterioration of the TPV	1.0% (1/100)	100.0% (NA)	98.9% (93.1%, 99.8%)	98.9% (93.1%, 99.8%)
Tricuspid regurgitation	1.0% (1/100)	100.0% (NA)	98.9% (93.1%, 99.8%)	98.9% (93.1%, 99.8%)
Valve dysfunction: mixed	1.0% (1/100)	100.0% (NA)	98.9% (93.2%, 99.8%)	98.9% (93.2%, 99.8%)
Embolization of the TPV	0.0% (0/100)	100.0% (NA)	100.0% (NA)	100.0% (NA)
Hemorrhage	0.0% (0/100)	100.0% (NA)	100.0% (NA)	100.0% (NA)
Nonstructural dysfunction	0.0% (0/100)	100.0% (NA)	100.0% (NA)	100.0% (NA)
Thrombosis of the TPV	0.0% (0/100)	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

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 19), 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 19: 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 with fragment embolization	4.2% (1/24) 0.0% (0/24)	6.6% (5/76) 1.3% (1/76)
Valve dysfunction: stenosis (all)	12.5% (3/24)	11.8% (9/76)
Valve dysfunction: regurgitation	8.3% (2/24)	6.6% (5/76)
Valve dysfunction: mixed	0.0% (0/24)	1.3% (1/76)
Valvular regurgitation, tricuspid	0.0% (0/24)	1.3% (1/76)
Prosthetic valve endocarditis	4.2% (1/24)	15.8% (12/76)
Pulmonary thromboembolism	0.0% (0/24)	1.3% (1/76)
Paravalvular leak: minor	4.2% (1/24)	0.0% (0/76)
Paravalvular leak: major	0.0% (0/24)	1.3% (1/76)
Structural deterioration of the TPV	0.0% (0/24)	1.3% (1/76)
Embolization of the TPV	0.0% (0/24)	0.0% (0/76)
Nonstructural dysfunction	0.0% (0/24)	0.0% (0/76)
Thrombosis of the TPV	0.0% (0/24)	1.3% (1/76)
Hemorrhage	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 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 91.0%.

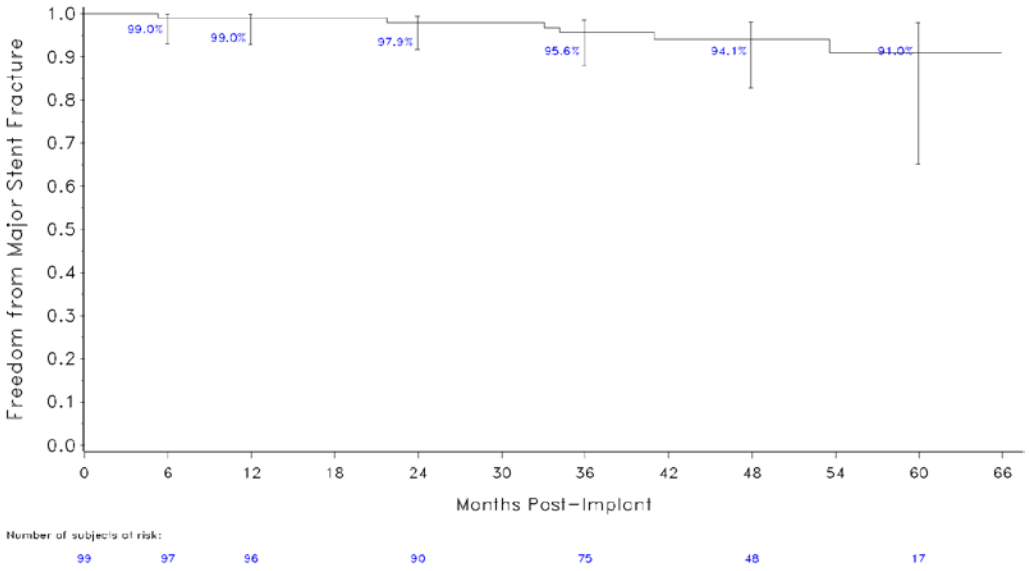

Figure 7: Kaplan-Meier freedom from major stent fracture – implanted >24 hours cohort (N = 99)

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 KM method.
3. 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 5 years postimplant was estimated to be 84.9%.

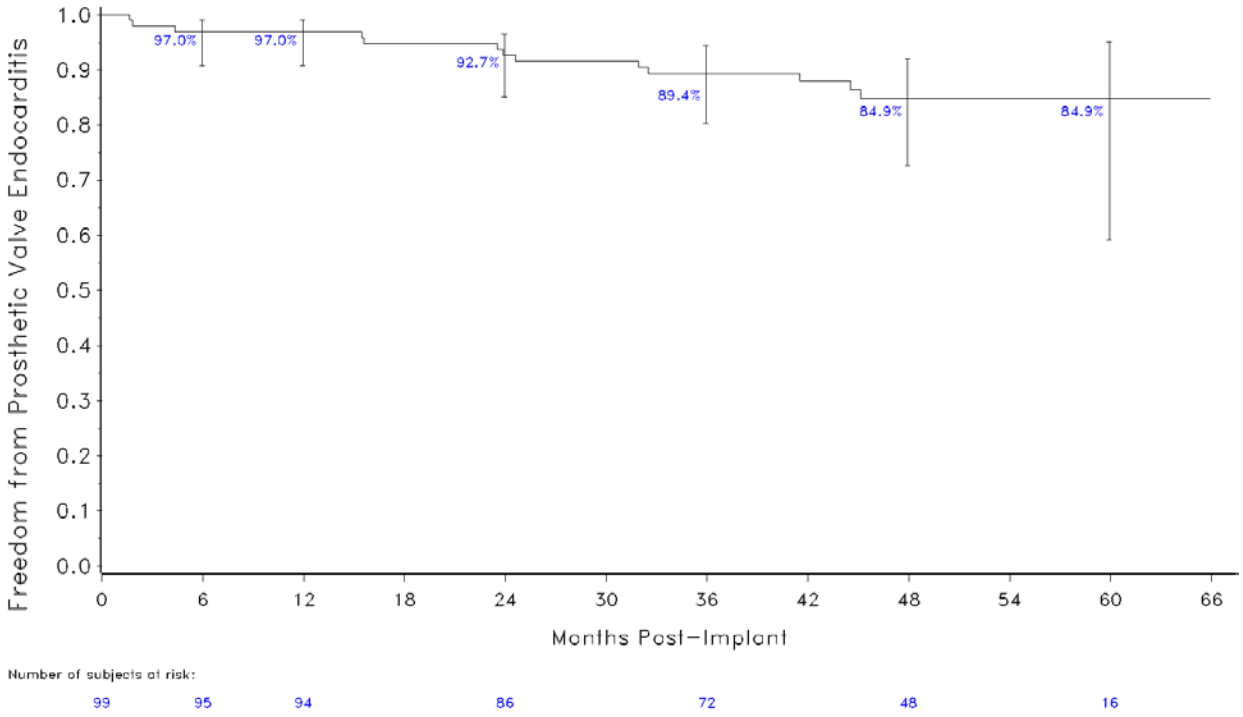

Figure 8: Kaplan-Meier freedom from prosthetic valve endocarditis – implanted >24 hours cohort (N = 99)

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 KM method.
3. 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 5 years postimplant was estimated to be 95.7%.

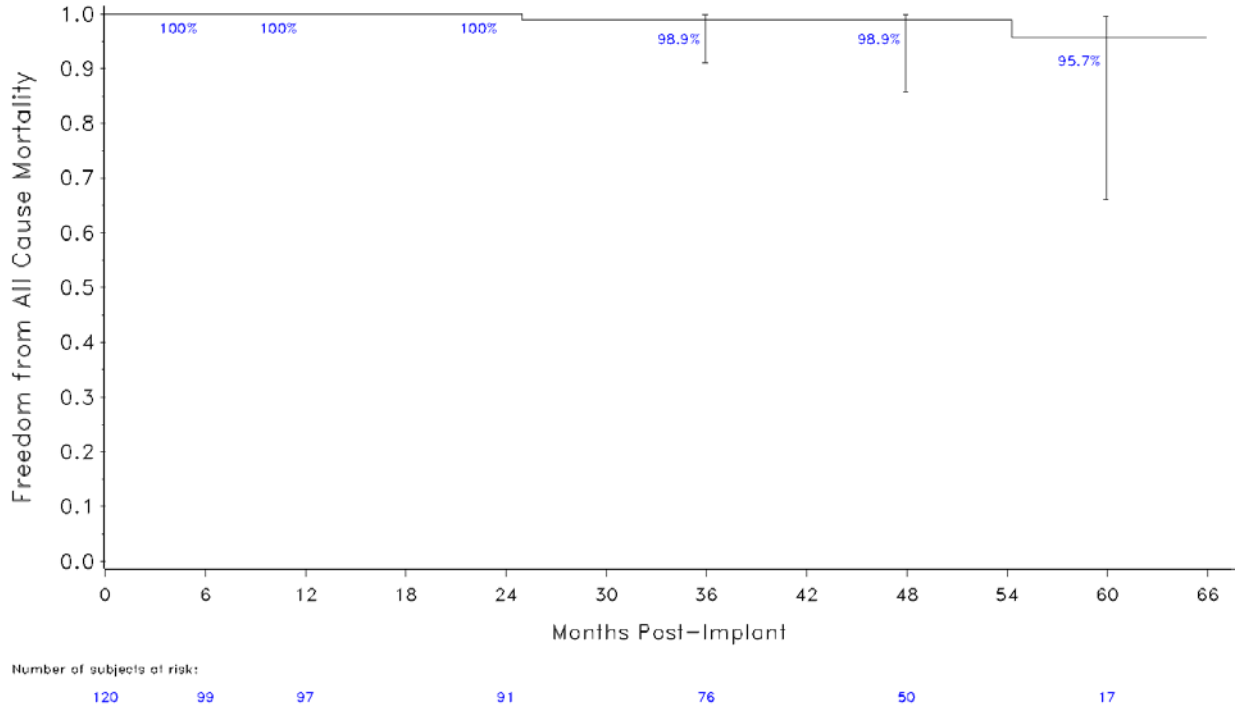

Figure 9: Kaplan-Meier freedom from all-cause mortality – catheterized cohort (N = 120)

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 KM method.
3. 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 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 postimplantation, less than mild pulmonary regurgitation by angiography postimplantation, and free of explant at 24 hours postimplantation. 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 20: New Enrollment PAS: procedural success – attempted implant cohort (N = 101)

	Implanted cohort (N = 101)
Procedural success	92.1% (93/101)
Procedural failure	7.9% (8/101)
Melody™ TPV not fixated within the desired location	0.0% (0/100)
RV-PA peak-to-peak gradient (measured in the catheterization lab) at least 35 mm Hg postimplant	0.0% (0/99)
More than trivial pulmonary regurgitation by angiography postimplant	6.0% (6/100)
Explant of the Melody™ TPV within 24 hours postimplant	1.0% (1/100)
Implant was aborted in 1 subject due to distal branch pulmonary artery perforation leading to pulmonary hemorrhage	1.0% (1/101)

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 5 years postimplant, freedom from TPV dysfunction was estimated to be 67.8%.

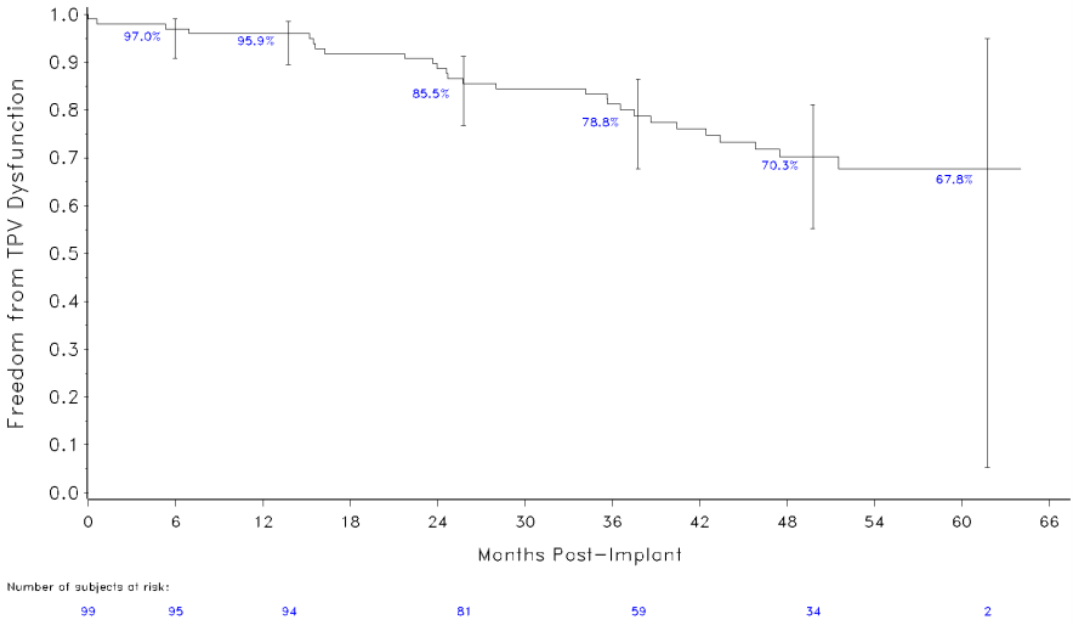

Figure 10: Kaplan-Meier freedom from TPV dysfunction – implanted >24 hours cohort (N = 99)

Notes:

1. 6 = 183 to 419 days, 12 = 420 to 785 days, 24 = 786 to 1150 days, 36 = 1151 to 1515 days, 48 = 1516 to 1880 days, and 60 = 1881 to 2245 days.
2. The cumulative probability of event-free estimate is based on the KM method.
3. 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.

10.2.4.3 Freedom from RVOT conduit reoperation

At 5 years postimplant, the freedom from RVOT conduit reoperation was estimated to be 81.9%. Ten subjects underwent RVOT conduit reoperation during follow-up.

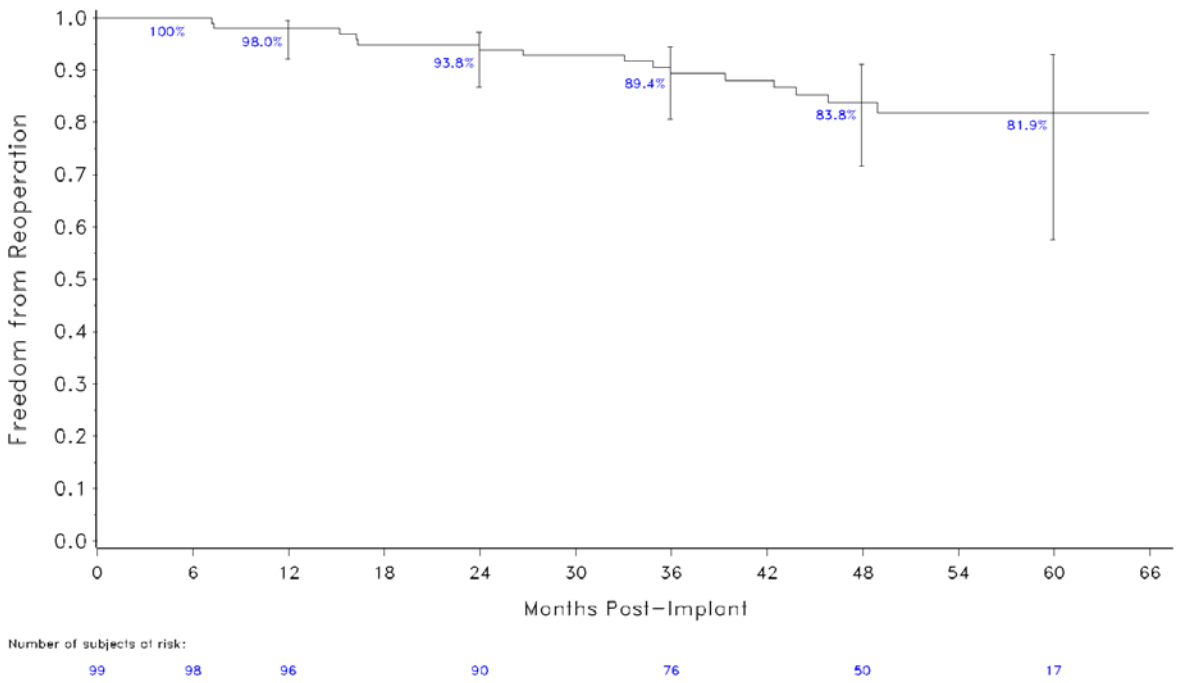

Figure 11: Kaplan-Meier freedom from RVOT conduit reoperation – implanted >24 hours cohort (N = 99)

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 KM method.
3. 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 catheter reintervention on the TPV

Freedom from catheter reintervention at 5 years postimplant was estimated to be 90.3%.

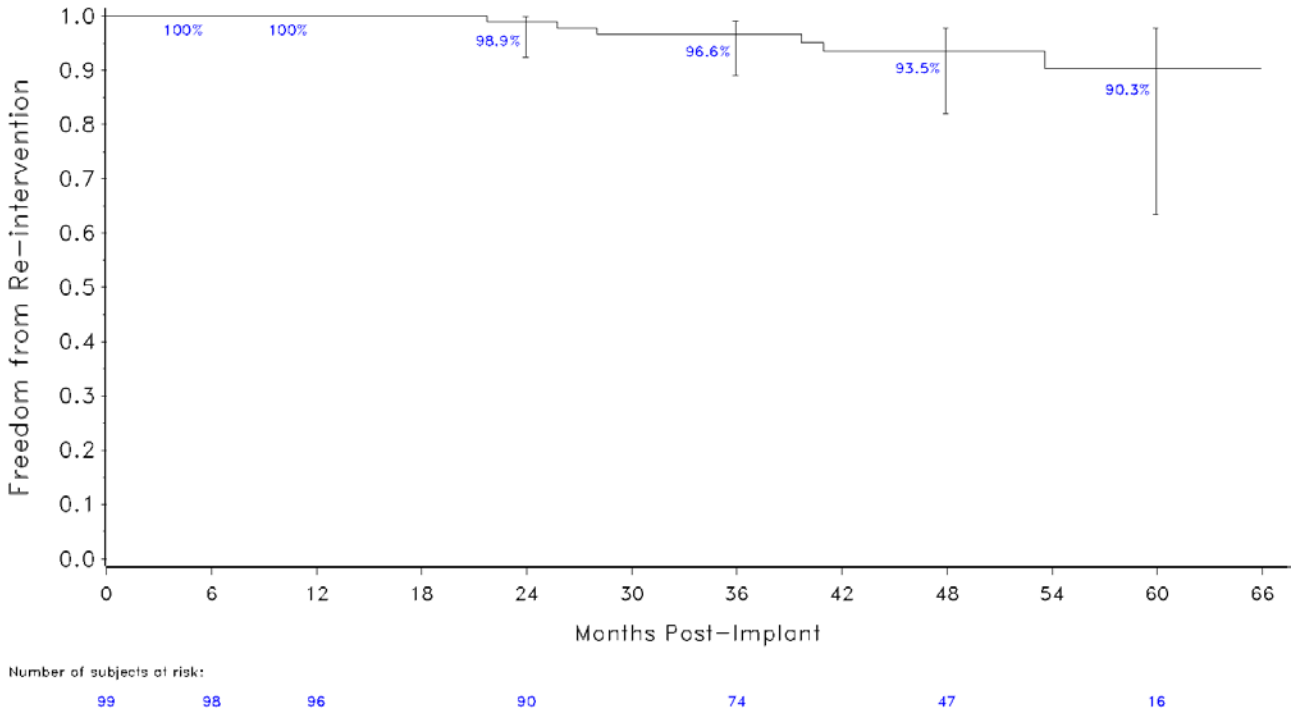

Figure 12: Kaplan-Meier freedom from catheter reintervention on the TPV – implanted >24 hours cohort (N = 99)

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 KM method.
3. 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.

10.2.4.5 Hemodynamic performance

At discharge and throughout 5 years of follow-up, the vast majority of subjects had no more than mild PR.

Table 21: New Enrollment PAS: pulmonary regurgitation by time interval – implanted >24 hours cohort (N = 99)

Degree of regurgitation[1, 2]	None	Trace	Mild	Moderate	Severe
Preimplant (n = 99)	2.0% (2/98)	6.1% (6/98)	7.1% (7/98)	40.8% (40/98)	43.9% (43/98)
Discharge (n = 99)	64.6% (62/96)	32.3% (31/96)	3.1% (3/96)	0.0% (0/96)	0.0% (0/96)
6 months (n = 97)	68.1% (64/94)	25.5% (24/94)	6.4% (6/94)	0.0% (0/94)	0.0% (0/94)
1 year (n = 91)	62.9% (56/89)	24.7% (22/89)	11.2% (10/89)	1.1% (1/89)	0.0% (0/89)
2 years (n = 61)	49.2% (29/59)	35.6% (21/59)	10.2% (6/59)	5.1% (3/59)	0.0% (0/59)
3 years (n = 57)	50.9% (27/53)	32.1% (17/53)	9.4% (5/53)	5.7% (3/53)	1.9% (1/53)
4 years (n = 32)	51.6% (16/31)	22.6% (7/31)	12.9% (4/31)	6.5% (2/31)	6.5% (2/31)
5 years (n = 10)	55.6% (5/9)	22.2% (2/9)	22.2% (2/9)	0.0% (0/9)	0.0% (0/9)

[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, 2 subjects at 1 year, 2 subjects at 2 years, 4 subjects at 3 years, 1 subject at 4 years, and 1 subject at 5 years postimplant.

Average RVOT mean gradient was 16.3 ± 7.1 mm Hg at discharge and remained clinically stable throughout follow-up, as shown in Table 22.

Table 22: New Enrollment PAS: RVOT mean gradient by time interval – implanted >24 hours cohort (N = 99)

RVOT mean gradient (mm Hg)[1]	n[2]	Mean ± SD	Median [min, max]	Q1, Q3
Preimplant (n = 99)	96	33.4 ± 14.1	34.3 [5.6, 70.0]	23.5, 43.0
Discharge (n = 99)	92	16.3 ± 7.1	15.4 [2.5, 40.0]	11.0, 20.0
6 months (n = 97)	91	15.0 ± 9.9	13.0 [3.0, 83.0]	10.0, 18.0
1 year (n = 91)	85	15.1 ± 7.1	13.0 [3.0, 34.0]	10.0, 20.0
2 years (n = 61)	54	15.5 ± 7.9	13.4 [2.8, 38.0]	9.7, 20.0
3 years (n = 57)	47	16.7 ± 10.8	14.0 [3.0, 55.0]	10.0, 20.0
4 years (n = 32)	25	12.8 ± 5.9	12.0 [2.0, 28.0]	9.0, 15.0
5 years (n = 10)	8	14.4 ± 12.6	10.0 [2.7, 40.0]	6.1, 20.0

[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, 7 subjects at 2 years, 10 subjects at 3 years, 7 subjects at 4 years, and 2 subjects at 5 years postimplant.

10.2.4.6 NYHA

Table 23 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.

Table 23: New Enrollment PAS: NYHA Functional Class by Time Interval – Implanted >24 hours Cohort (N = 99)

NYHA classification[1]	I	II	III	IV
Baseline (N = 99)	35.1% (34/97)	49.5% (48/97)	14.4% (14/97)	1.0% (1/97)
1 year (N = 92)	88.9% (80/90)	10.0% (9/90)	0.0% (0/90)	1.1% (1/90)
2 years (N = 84)	82.1% (64/78)	16.7% (13/78)	1.3% (1/78)	0.0% (0/78)
3 years (N = 84)	79.7% (63/79)	16.5% (13/79)	2.5% (2/79)	1.3% (1/79)
4 years (N = 58)	76.5% (39/51)	17.6% (9/51)	5.9% (3/51)	0.0% (0/51)
5 years (N = 29)	85.2% (23/27)	11.1% (3/27)	3.7% (1/27)	0.0% (0/27)
[1] NYHA was unable to be assessed for 2 subjects at baseline, 2 subjects at 1 year, 6 subjects at 2 years, 5 subjects at 3 years, 7 subjects at 4 years, and 2 subjects at 5 years postimplant.				

10.2.4.7 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 6 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 >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 24 , Table 25, and Table 26.

Table 24: 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 25: 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 26: 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.					

10.3 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 27 presents the subject demographics and baseline characteristics of the enrolled subjects in the pooled dataset. The baseline demographics were generally similar in the 2 studies (Table 5 and Table 21), with the exceptions that bioprosthetic valve targets and a mixed indication (stenosis and regurgitation) were proportionately more frequent in the New Enrollment PAS.

Table 27: Pooled subjects demographics – enrolled cohort (N = 302)

Assessment	Enrolled cohort (N = 302)
Gender	
Female	35.8% (108/302)
Male	64.2% (194/302)
Age (years)	
n	302
Mean ± SD	21.1 ± 9.8
Median [min, max]	18.0 [5.0, 53.0]
Original diagnosis	
Aortic valve disease (Ross)	19.2% (58/302)
Double outlet right ventricle	6.0% (18/302)
Isolated pulmonary stenosis	2.6% (8/302)
Pulmonary atresia	1.7% (5/302)
Tetralogy of Fallot	45.7% (138/302)
Transposition of the great arteries	9.3% (28/302)
Truncus arteriosus	12.6% (38/302)
Other[1]	3.0% (9/302)
RVOT conduit type	
Homograft	70.9% (214/302)
Biological valved conduit	16.6% (50/302)
Bioprosthesis	8.6% (26/302)
Synthetic	4.0% (12/302)
Other	0.0% (0/302)
RVOT conduit size (mm) when originally implanted	
n	275
Mean ± SD	21.0 ± 2.9
Median [min, max]	21.0 [11.0, 30.0]
Bioprosthesis size (mm) when originally implanted	
n	26
Mean ± SD	23.7 ± 3.0
Median [min, max]	23.0 [18.0, 31.0]
Primary indication	
Stenosis	24.2% (71/293)
Regurgitant	51.2% (150/293)

Assessment	Enrolled cohort (N = 302)
Mixed	24.6% (72/293)
Pulmonary regurgitation by site echo	
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)	
n	292
Mean ± SD	32.7 ± 14.4
Median [min, max]	33.5 [5.2, 97.0]

[1] Other original diagnoses included: 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); situs ambiguus asplenia, dextrocardia, and AV canal (n = 1); 22q11 deletion, mesocardia, posterior malalignment VSD with coarctation of the aorta (n = 1); CHARGE association (AVSD, pulmonary atresia) (n = 1); interrupted aortic arch (IAA), ASD, VSD, sub-aortic stenosis (n = 1); pulmonary stenosis with VSD (n = 1); IAA and VSD (n = 1); pulmonary stenosis, sinus venosus ASD, interrupted inferior vena cava, sick sinus syndrome, VSD (n = 1).

10.3.2 Pooled safety results

10.3.2.1 Acute procedure-related serious adverse events

Table 28 provides a summary of the pooled procedure-related adverse events. RVOT conduit rupture or dissection was the most common serious adverse event, occurring in 3.1% of the patients.

Table 28: Summary of pooled acute procedure-related serious adverse events (N = 287)

Procedure-related serious adverse event	Subjects with event (N = 287)
Subjects with procedure-related SAEs	7.7% (22/287)
RVOT conduit rupture or dissection	3.1% (9/287)
Perforation of vessel	1.0% (3/287)
Catheter induced arrhythmia	0.7% (2/287)
Hemothorax	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 respiratory/pulmonary	0.7% (2/287)
Other cardiac event	0.3% (1/287)
Other central nervous system	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 29 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 29: 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	14.8% (37/250)
Stent fracture: major	7.6% (19/250)
Valve dysfunction: stenosis	2.8% (7/250)
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)

10.3.3 Pooled safety and effectiveness outcome measures

Table 30 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 92.1%. Freedom from reoperation, catheter reintervention on the TPV, major stent fracture, and mortality were all above 97.0%.

Table 30: 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	246	0.9216 (0.8615, 0.9569)
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, and 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.

10.4 Dysfunctional bioprosthetic valve – summary of safety and effectiveness measures

Medtronic has collected clinical data to establish reasonable assurance of safety and effectiveness of the Melody TPV implanted into a dysfunctional surgical bioprosthetic valve in the pulmonary position from the following three 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

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 surgical 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.

10.4.1 Subject Demographics

Table 31 presents the subject demographics and baseline characteristics analyzed for enrolled subjects. The population consisted of 68 male and 57 female subjects with a mean age of 24.5 ± 12.3 (range 7 to 79 years). Tetralogy of Fallot was the most common original diagnosis (72.8%).

Table 31: 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
Median [Min, Max]	22.0 [5.0, 79.0]
Q1, Q3	15.0, 31.0
Original Diagnosis[1]	
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 venticular septum	4.0% (5/125)
With ventircular 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)

Table 31: Subject Demographics and Baseline Characteristics

Assessment	Result (N=125)
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
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
# of Previous Bioprosthetic Valves	
0	15.3% (19/124)
1	66.1% (82/124)
2	13.7% (17/124)
3	4.0% (5/124)

Table 31: Subject Demographics and Baseline Characteristics

Assessment	Result (N=125)
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).

10.4.2 Procedural Data

A summary of procedural data is provided in Table 32. The percutaneous femoral venous approach was used in the majority of subjects (95.2%); however, in some patients, internal jugular vein (4.8%) access was used. The majority of subjects did not undergo any concomitant procedures (68.8%).

Table 32: 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 Procedures[1]	
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]

Variable	Result (N=125)
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	
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)

[1] Subjects may have had more than one concomitant procedure.
[2] Other 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).

10.4.3 Safety Results

10.4.3.1 Acute Procedure-related Serious Adverse Events

Of the 125 subjects implanted, 5 (4.0%) experienced acute serious adverse events classified as either possibly or definitely related to the procedure.

Table 33: 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)
Hemorrhage: major	0.8% (1/125)
Hemorrhage: minor	0.0% (0/125)

Procedure-Related Serious Adverse Event	Result (N=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

10.4.3.2 Device-related Serious Adverse Events

Of the 125 subjects implanted, 3 (2.4%) experienced acute serious adverse events classified as either possibly or definitely related to the device.

Table 34: 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)
Pneumonia	0.0% (0/125)
Pulmonary thromboembolism	0.0% (0/125)
Sepsis, confirmed (positive blood culture)	0.0% (0/125)

Device-Related Serious Adverse Event	Result (N=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**

10.4.4 Effectiveness Results

10.4.4.1 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. Of the 125 subjects implanted, 88.9% had a procedural success as shown in Table X. All valves delivered remained in the desired implant location; however, 1 subject had a RV-PA peak-to-peak gradient >35 mm Hg and 12 subjects had mild or greater PR by angiography.

Table 35: 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)

[1]One or more elements of procedural success were not able to be determined for 8 subjects.

10.4.4.2 Freedom from TPV Dysfunction

TPV dysfunction is a composite outcome, defined as 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 1 year postimplant, freedom from TPV dysfunction was estimated to be 97.4% among available subjects.

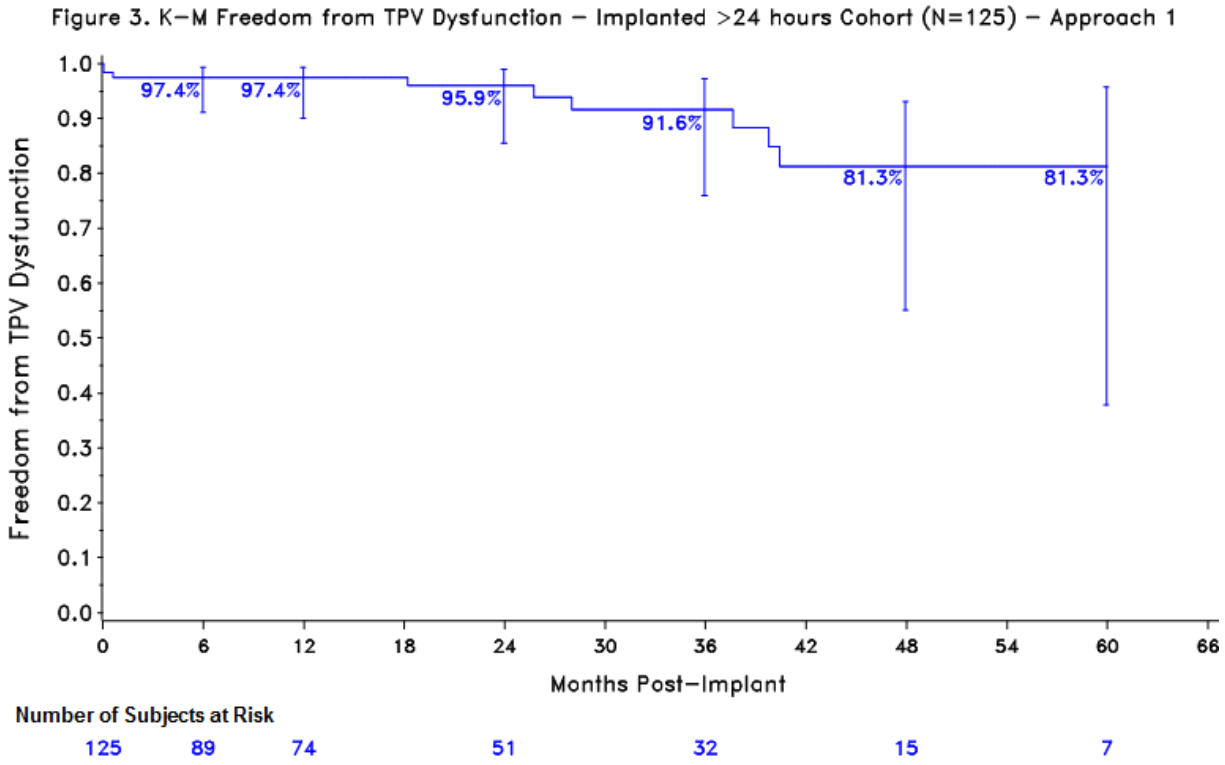

Figure 13: Kaplan-Meier freedom from TPV dysfunction – implanted >24 hours cohort (N = 125)

Notes:

1. The cumulative probability of event free estimate is based on the K-M 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.

10.4.4.3 Freedom from Reoperation

At 1 year postimplant, the freedom from reoperation was estimated to be 100%. One subject underwent reoperation over 2.5 years post-implant.

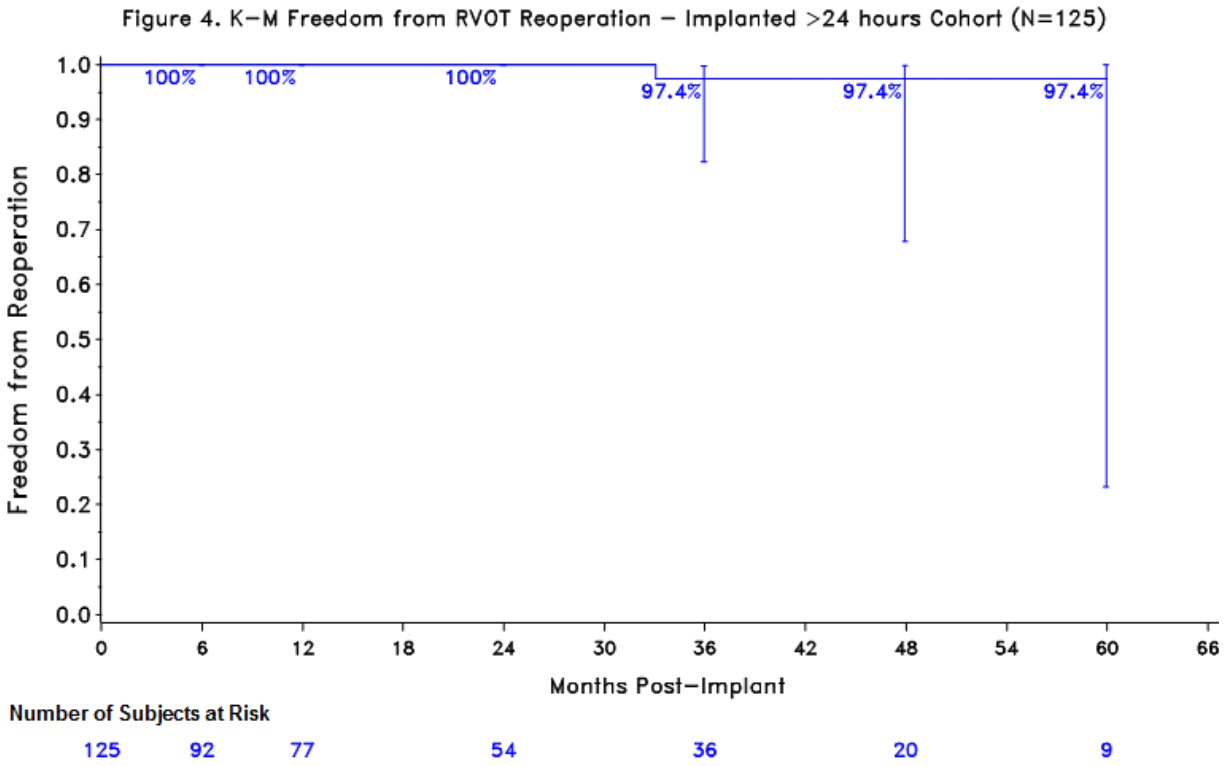

Figure 14: Kaplan-Meier freedom from reoperation – implanted >24 hours cohort (N = 125)

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 KM method.
3. 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.

10.4.4.4 Freedom from Catheter Re-intervention on the TPV

Freedom from catheter reintervention at 1 year postimplant was estimated to be 100%. Two subjects underwent catheter reintervention over 2 years post-implant.

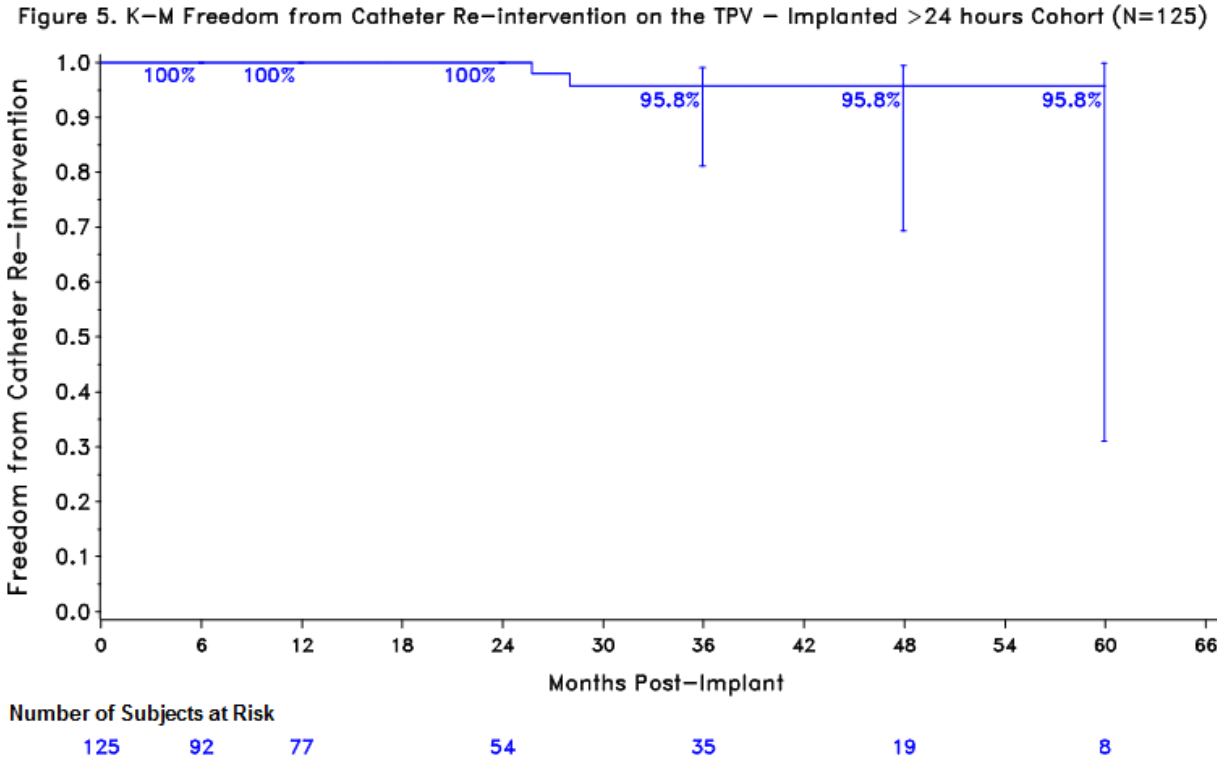

Figure 15: Kaplan-Meier freedom from catheter reintervention on the TPV – implanted >24 hours cohort (N = 125)

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 KM method.
3. 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.

10.4.4.5 Hemodynamic Performance

The distribution of degree of pulmonary regurgitation and average mean RVOT gradient +/- one standard deviation are shown in Figures 16 and 17, respectively.

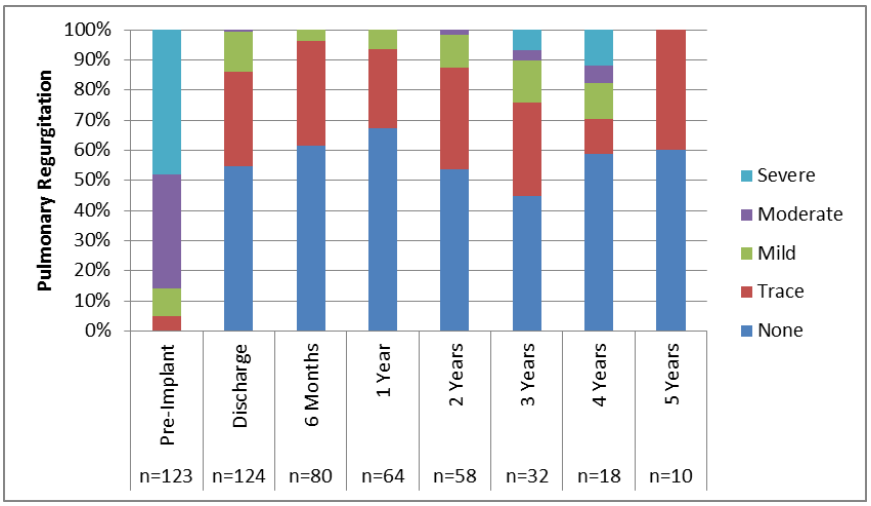

Figure 16: Pulmonary Regurgitation

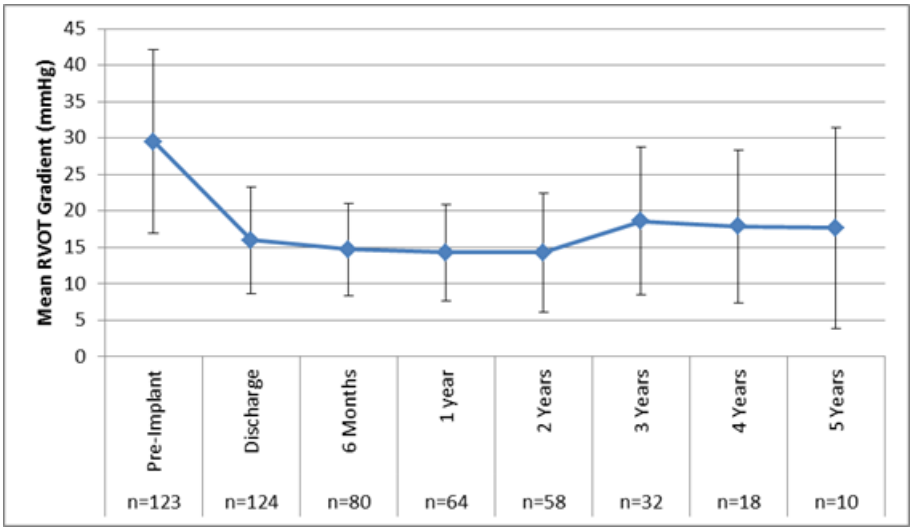

Figure 17: Mean RVOT Gradient

11.0 Disclaimer of warranty

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