

New Humanitarian Device Approval

Medtronic Melody® Transcatheter Pulmonary Valve



FDA approved this device under the Humanitarian Device Exemption (HDE) program <http://www.fda.gov/cdrh/ode/hdeinfo.html>. See the links below to the Summary of Safety and Probable Benefit (SSPB) and other sites for more complete information on this product, its indications for use, and the basis for FDA's approval.

Product Name: Medtronic Melody® Transcatheter Pulmonary Valve (Model PB10) and Medtronic Ensemble® Transcatheter Valve Delivery System (NU10)

Manufacturer: Medtronic Heart Valves, Inc.

Address: 1851 Deere Avenue, Santa Ana, California 92705

Approval Date: 25 January 2010

Approval Letter: A link to web for the approval letter

What is it?

The Medtronic Melody® Transcatheter Pulmonary Valve is a manufactured replacement pulmonary heart valve that had already been previously repaired. The pulmonary valve is one of four valves in the human heart that help pump blood throughout the body. The Melody valve is made from a cow's jugular vein valve that is sewn into a small metal stent (scaffolding). The Melody valve comes in sizes 18, 20, and 22mm diameters and has a stent length of 28mm. The Medtronic Ensemble® Transcatheter Valve Delivery System is a catheter (long tube with small diameter) that helps guide the Melody into the heart. The Ensemble delivery system has catheters with balloon sizes of 18, 20, and 22mm.

How does it work?

The Melody heart valve is first crimped down onto the Ensemble delivery catheter's balloon and then is fished through a vein in the groin and into the right side of the heart where it is placed into position within the pulmonary valve. The small balloon is then inflated to open up the Melody valve into position, the catheter is removed from the body, and the Melody immediately becomes the new pulmonary valve.

When is it used?

The Melody is used to repair a stenosed (blocked) or regurgitant (leaky) pulmonary heart valve that has previously been replaced to correct congenital (birth) heart defects. The Melody is put in place without using open heart surgery and while the heart is beating.

What will it accomplish?

The Melody will replace a poorly functioning, previously repaired, pulmonary valve in children and adults who will need multiple open heart surgeries in their lifetime. The Melody will repair pulmonary valve function without open heart surgery and may lengthen the time until the patient needs another open heart surgery.

When should it not be used?

This valve should not be placed into the aortic or mitral heart valve positions or if the heart has an infection.

Additional information:

SSPB and Labeling: The SSPB is not yet available and that a link will be established when the SSPB is posted to the web.

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Concurrence:

HDE Number: H080002

N.B.

Summary of Safety and Probable Benefit

Melody® Transcatheter Pulmonary Valve
Ensemble® Transcatheter Valve Delivery System

I. General Information

Device Generic Name: Pulmonary Valve
Balloon catheter

Device Trade Name: Melody® Transcatheter Pulmonary Valve
Ensemble® Transcatheter Valve Delivery System

Applicant's Name and Address: Medtronic, Inc.
1851 E. Deere Avenue
Santa Ana, CA 92705

Humanitarian Device Exemption
(HDE) Number: H080002

Humanitarian Use Device (HUD) #: 07-0180

Date of Humanitarian Use Device
Designation: July 10, 2007

Date of Panel Recommendation: July 22, 2009

Date of GMP Inspection: N/A -- no inspection required

Date of Notice of Approval: 25 January 2010

Note: The Melody® valve and Ensemble® delivery system are designed to be used in conjunction with each other as a system. Throughout this document the Melody device is referred to interchangeably as the Melody device, Melody valve, valve, or TPV (transcatheter pulmonary valve). Melody® and Ensemble® are registered trademarks of Medtronic, Inc.

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II. Indications for Use

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

- Existence of a full (circumferential) RVOT conduit that was equal to or greater than 16 mm in diameter when originally implanted and
- Dysfunctional RVOT conduits with a clinical indication for intervention, and either:
 - regurgitation: \geq moderate regurgitation, or
 - stenosis: mean RVOT gradient \geq 35 mm Hg

III. Contraindications

There are no known contraindications for the Melody TPV.

IV. Warnings and Precautions

The warnings and precautions can be found in the *Instructions for Use*.

Warnings

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

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

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

Procedural Warnings

- Assessment of the coronary artery anatomy for the risk of coronary artery compression should be performed in all patients prior to deployment of the TPV.
- To minimize the risk of conduit rupture, do not use a balloon with a diameter greater than 110% than the nominal diameter (original implant size) of the conduit for pre-dilation of the intended site of deployment, or for deployment of the TPV.

Valve-Related Warnings

- The potential for stent fracture should be considered in all patients who undergo TPV placement. Radiographic assessment of the stent with

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chest radiography or fluoroscopy should be included in the routine postoperative evaluation of patients who receive a TPV.

- 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.

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

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

DO NOT use the device if:

- it has been dropped, damaged, or mishandled in any way;
- the 'Use By' date has elapsed;
- the tamper evident seal is broken;
- the serial number tag does not match the container label;
- it has been exposed to freezing or prolonged heat (Check freeze indicator. If exposed to a freeze-thaw condition, the indicator vial will break, causing the dye to escape and stain the paper backing.); or
- the storage solution does not completely cover the device.

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

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

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

DO NOT attempt to repair a damaged device.

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

DO NOT use forceps to manipulate the stent.

DO NOT overexpand the device beyond the maximum recommended size, which is 22-mm, as this may result in a regurgitant TPV.

Caution: Exposure to glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure or breathing of the chemical vapor. Use only with adequate ventilation. If skin contact occurs,

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immediately flush the affected area with water (minimum of 15 minutes). In the event of eye contact, flush with water for a minimum of 15 minutes and seek medical attention immediately.

Delivery System-Related Warnings

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

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

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

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

Other Warnings

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

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

Precautions

- Rinsing procedures of the TPV must be strictly followed.
- The sealed catheter packaging should be inspected prior to opening. If the seal is broken or the packaging is damaged or wet, sterility cannot be assured.
- Proper functioning of the catheter depends on its integrity. Care should be used when handling the catheter. Damage may result from kinking, stretching, or forceful wiping of the catheter.
- This catheter is not recommended for pressure measurement or delivery of fluids.
- Careful attention must be paid to the maintenance of tight catheter connections and to utilizing aspiration before proceeding to avoid air introduction into the system.
- The delivery system must be carefully flushed to avoid the introduction of air bubbles.
- Before crimping (reducing) the size of the valve on the balloon, the orientation should be verified. (The blue suture should be adjacent to blue tip of the catheter.)

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- Do not remove the tag attached to the valve until the valve is ready to be crimped onto the delivery system, and implantation is imminent. This tag, along with the blue suture, identifies the outflow end of the valve and helps with proper orientation of the TPV on the delivery system.
- The inflation diameter of the balloon used during valve delivery should approximate the diameter of the obstructive vessel and the intended implant site.
- The crimping procedure must be carried out carefully. While crimping, the orientation of the TPV in the stent must be known at all times. No change of orientation should occur as the valve is mounted on the balloon. Do not place excessive pressure on the device during crimping.
- Use of 2 inflation devices (1 for each balloon) with pressure gauges is highly recommended during this procedure when inflating the balloon to deliver the valve.
- The TPV is rigid and may make navigation through vessels difficult.
- Balloon deployment should be conducted under fluoroscopic guidance with appropriate X-ray equipment.
- Ensure the balloons are completely deflated before pulling the catheter back into the sheath.
- If resistance is felt upon attempted removal of the Ensemble Transcatheter Valve Delivery System, check to make sure 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, be sure to maintain guidewire position and gently withdraw the delivery system using a twisting action under fluoroscopic observation. If the balloon catheter has seized, and the guidewire cannot be withdrawn, then a second venous line should be inserted, a catheter directed through the expanded Melody TPV, and a second guidewire placed in the pulmonary artery. The original Ensemble Transcatheter Valve Delivery System and guidewire can then be carefully removed together under fluoroscopic guidance.

V. Device Description

Melody Transcatheter Pulmonary Valve (TPV)

The TPV consists of a segment of bovine jugular vein with a thinned down venous wall containing a native, central, competent venous valve (Figure 1A and Figure 1B). This bovine vein is attached to a Platinum/Iridium stent with a length of 28 mm and a diameter of 18 mm that can be crimped to a size of 6 mm and re-expanded up to 22 mm (Figure 1C). The stent geometry has an eight-crown zig pattern with six segments along its length. The venous

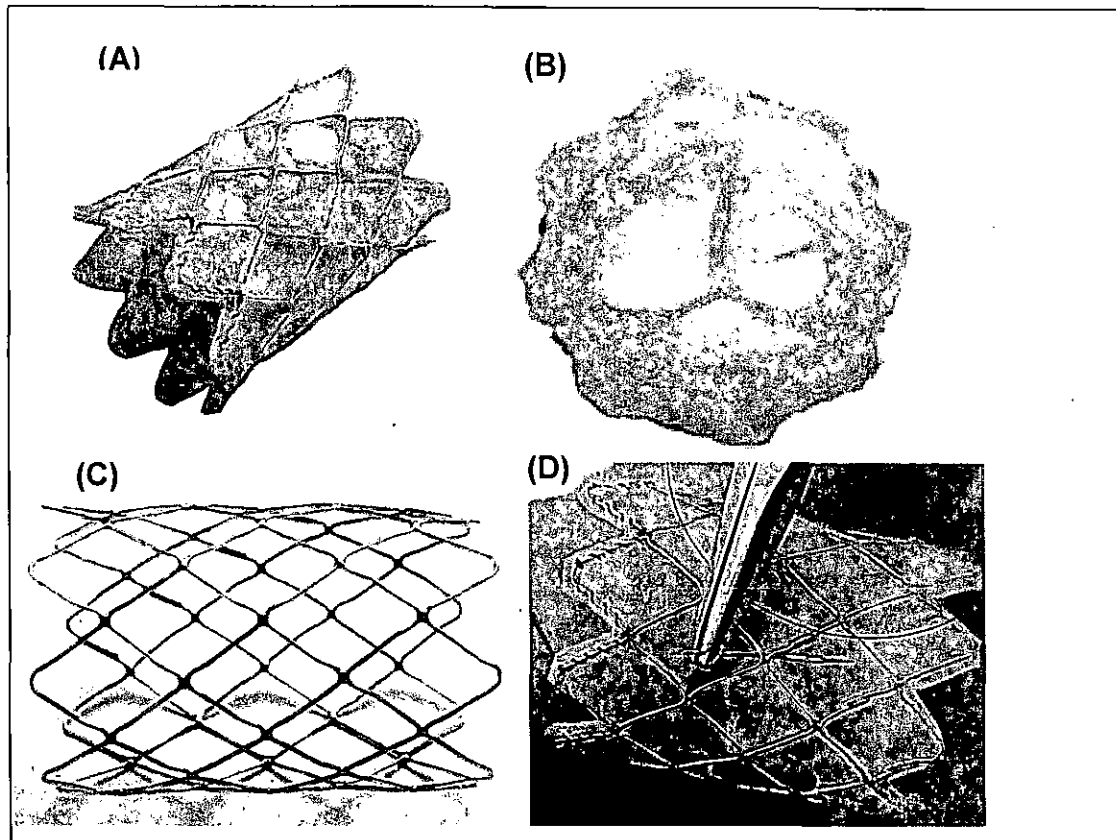
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segment is attached to the stent around its entire circumference at the inflow and outflow and discretely at each node of the stent between the inflow and outflow suture lines. The venous segment is sewn to the stent using polypropylene sutures. The suture is clear for all suture points except the outflow line, which is blue to signify the outflow end of the device (Figure 1D).

The venous segment is fixed in a buffered glutaraldehyde solution in concentration low enough to preserve the flexibility of the venous valve leaflets. A final sterilization step is performed on the combined device using a proprietary sterilant containing glutaraldehyde and isopropyl alcohol as the active ingredients.

Figure 1: The Melody Transcatheter Valve



Ensemble Transcatheter Valve Delivery System Description

The Ensemble Transcatheter Valve Delivery System (available in three sizes: 18, 20 and 22 mm diameter outer balloon) is designed to allow a physician to deliver a mounted Melody Transcatheter Pulmonary Valve from the femoral

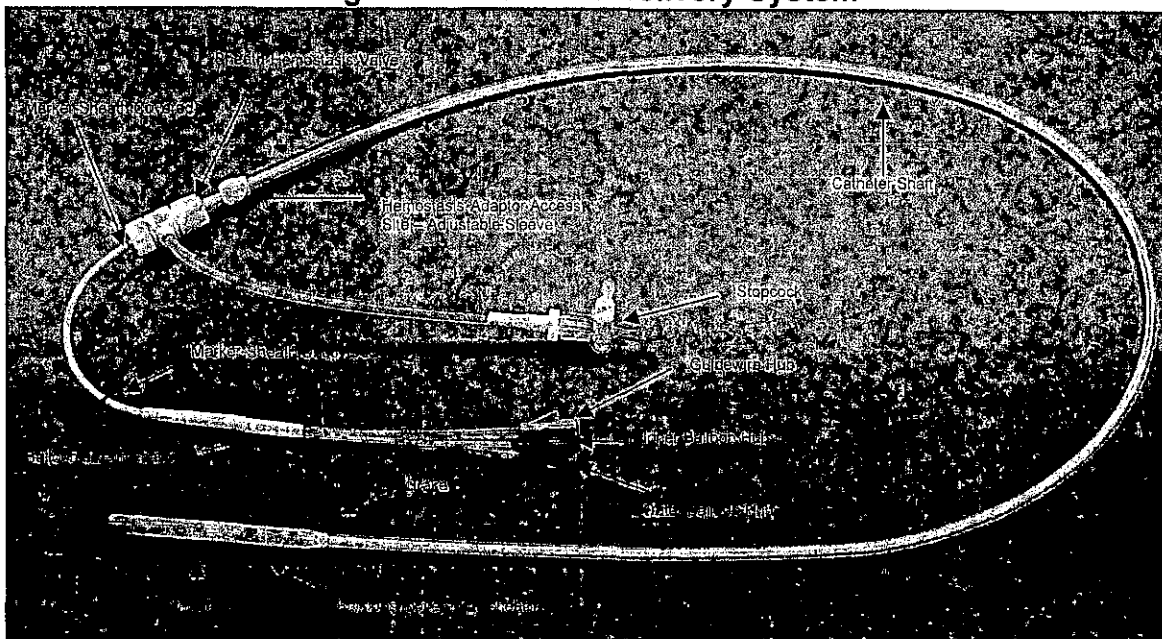
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vein to the area of a failed pulmonary conduit previously placed surgically for the repair of congenital pathologies.

The Ensemble Valve Delivery System is a double balloon dilation catheter permanently mounted in a 15F, 90cm long sheath. The distal 7 cm of the sheath is expanded to 20F ID/22Fr OD to accommodate front loading of the valve. The obturator tip is approximately 4 cm in length with a conical shape for easy introduction into the skin and tracking to the delivery site. The hemostasis valve (on the sheath) with side arm and stopcock allows flushing of the sheath.

Figure 2: Ensemble Delivery System



There are three extensions with luer fittings at the proximal end (one lumen for inflation of the inner balloon, one lumen for inflation of the outer balloon, and one lumen for the guidewire). The crossing profile of the system is 22F. A ring of material is bonded to the catheter shaft proximal to the outer balloon that acts as a brake keeping the catheter from retracting into the sheath. The Melody device is mounted onto the balloon catheter delivery system for deployment to the pulmonary implant site via femoral venous access. The delivery system utilizes a balloon catheter with a balloon-in-balloon design that allows for accurate placement of the device. The catheter design is compatible with a .035" guidewire.

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Deployment Procedure

The deployment of the Melody device utilizes common interventional cardiology techniques that are currently used in placement of stents for coronary and intravascular applications. The Ensemble Delivery System has features that are similar to existing balloon and self-expanding stent delivery systems. The Ensemble Transcatheter Valve Delivery System is used with the Melody Pulmonary Valve to implant a functioning valve into a dysfunctional conduit.

The Melody valve is stored in a glutaraldehyde and isopropyl alcohol solution. The valve is then rinsed in saline solution and the serial number tag is removed. The valve is then hand-crimped (by crimping it on mandrels of increasingly smaller sizes) and loaded onto the Ensemble delivery system.

The delivery system is then navigated through the venous system from a femoral venous puncture to the pulmonary artery over a stiff guidewire. Once positioned, the sheath is retracted to expose the Melody valve; next, the balloons are expanded (inner first, then outer) to position the Melody valve. The balloons are then deflated and the delivery system is removed.

VI. Alternative Practices and Procedures

Surgical placement of an RV to PA conduit is the procedure of choice for palliation of RV outflow tract obstruction for many forms of complex congenital heart disease. Non-surgical alternatives to pulmonary valve repair/replacement include balloon angioplasty and percutaneous stent implantation.

VII. Marketing History

The Melody/Ensemble system has a CE Mark in the European Union (received: September 2006). Additionally, the system has a Medical Device License in Canada (received: December 2006).

The Melody/Ensemble system has not been withdrawn from any market for any reason relating to the safety and effectiveness of the device.

VIII. Adverse Events

Observed Adverse Events

The following clinical data are safety results from an ongoing prospective, non-randomized, multi-center evaluation being conducted at five centers in the United States. These data were obtained from 99 subjects who were catheterized for potential implantation with the TPV from January 31, 2007

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through December 12, 2008. Of these 99 catheterized subjects, implantation was performed in 90.

Four of the 99 catheterized subjects (4%) experienced serious intra-procedure-related serious adverse events (Table 1). Procedural mortality was 1.0%.

Table 1: Procedure-related serious adverse events

Subject	Event Description	Treatment	Outcome
1	Conduit rupture	Emergent surgical conduit exchange; Melody TPV explanted	Resolved without sequelae
2	Dissection of a coronary artery during coronary arteriography; cardiac arrest.	Coronary stent placement, ECMO	Died on post-procedure day 20
3	Perforation of small branch of pulmonary artery	Coil embolization	Resolved without sequelae
4	Wide-complex tachycardia	Cardioversion	Resolved without sequelae

The mean follow-up through March 27, 2009 was 9.2 ± 5.7 months (range 0 to 25.5 months). There was no additional mortality during follow-up. Device-related adverse events that were observed in follow-up are summarized in Table 2.

Table 2: Summary of device-related adverse events during follow-up (N=89 subjects implanted >24 hours)

Event	Subjects with Event N (%)	Freedom from Event at 6 months (SE)	Freedom from Event at 12 months (SE)
Stent Fracture (All)	16 (18%)	89.3 (4.3)%	77.1 (7.5)%
Minor stent fracture	11 (12%)	94.3 (3.2)%	84.1 (6.7)%
Major stent fracture	5 (6%)	98.8 (1.5)%	90.6 (5.2)%
Valve dysfunction: stenosis	6 (7%)	94.9 (3.0)%	90.5 (4.8)%
Worsening of tricuspid regurgitation associated with right heart failure	1 (1%)	100 (--)%	100 (--)%
Reintervention	6 (7%)	98.8 (1.5)%	93.5 (4.3)%
Reoperation (conduit exchange)	1 (1%)	98.6 (1.6)%	98.6 (2.2)%

Notes:

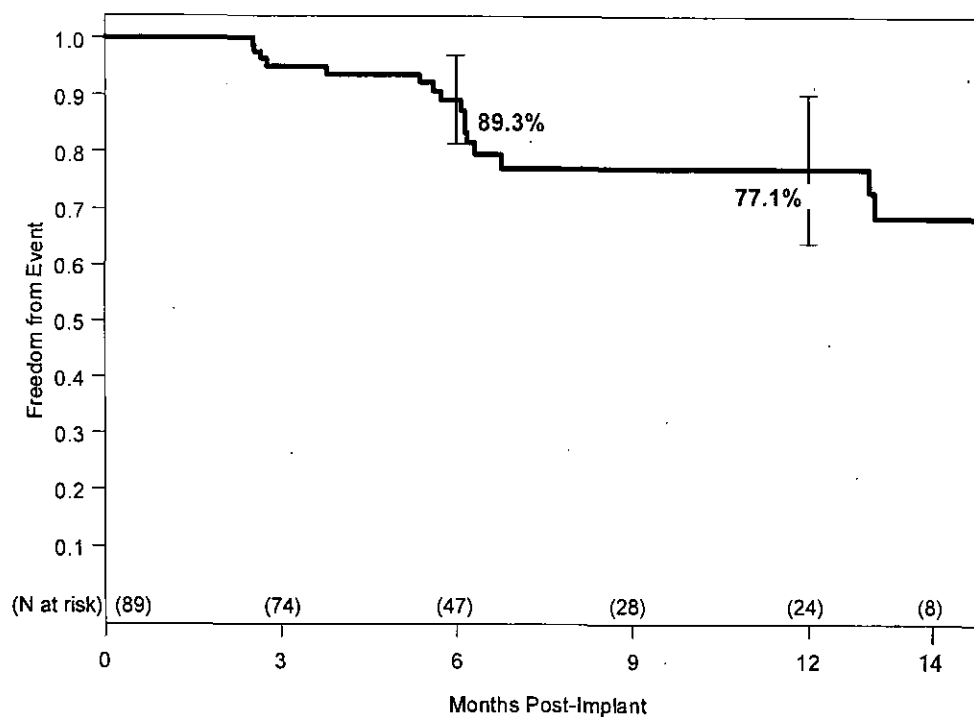
1. Stent fractures that required intervention were defined as major; stent fractures not requiring intervention were defined as minor.
2. Valve dysfunction: stenosis defined as mean RVOT gradient >40 mmHg by Doppler echocardiography.
3. Re-interventions were balloon angioplasty in one subject, and repeat implantation of a second TPV in 5 subjects
4. One subject underwent re-implantation of a second TPV, followed by reoperation two months later.

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Stent fractures were detected at radiographic follow-up in 16 subjects (18%) during the follow-up period. Overall freedom from stent fracture was 89.3% (SE = 4.3%) at 6 months and 77.1% (SE = 7.5%) at 12 months (Figure 3). In five subjects, stent fracture was associated with recurrent obstruction that was treated with re-implantation of a second TPV. One of these 5 subjects ultimately had surgical conduit exchange 2 months after implantation of their second TPV.

Figure 3: Freedom from Stent Fracture



Note:

The error bars are the 95% confidence intervals at 6 months and 12 months, respectively.

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Potential Adverse Events

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

- rupture of the RVOT conduit
- compression of a coronary artery
- perforation of a major blood vessel
- embolization or migration of the TPV
- perforation of a heart chamber
- arrhythmias
- allergic reaction to contrast media
- cerebrovascular events (TIA, CVA)
- infection/sepsis
- fever
- hematoma
- radiation-induced erythema
- pain at the catheterization site

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

- 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

IX. Summary of Preclinical Studies

The following *in vitro* testing was performed on the Platinum/Iridium stent component and showed acceptable results: radial strength, corrosion, foreshortening, recoil, mechanical characterization, fatigue/durability analysis, and magnetic resonance imaging compatibility. Additionally, the following tests were performed for the Ensemble delivery system and showed acceptable results: mechanical characterization bond strength, diameter and profile, hemostasis, balloon compliance, and simulated use.

Table 3 summarizes the important structural and hydrodynamic performance *in vitro* testing performed on the Melody device.

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Table 3: *In vitro* Test Summary

Test/Controls	Study Objectives	Results
Steady Forward Flow	To determine the pressure drop at various steady-state flow rates	The steady flow mean pressure drop increased non-linearly as the cardiac output increased. These results are expected for this device.
Pulsatile Flow	To provide pulsatile flow data for pressure drop, effective orifice area (EOA) and dynamic regurgitation performance	<p>Pressure Drop: Pressure drop as a function of flow rate results are similar for both the test and controls.</p> <p>Dynamic Regurgitation: total regurgitant volume for all valves (test/control) were < 7 mL/beat. Regurgitation decreased with the increase in beat rate.</p> <p>Leakage Volume as a function of Back Pressure: test devices had similar leakage volumes (< 5mL/beat) at each back pressure.</p> <p>EOA: EOA for the controls increased as flow rates increased. The test device EOAs were similar across all flow rates.</p>
Steady Backflow Leakage	To determine the leakage rate at various steady back flow pressures	For both the test and controls, the amount of leakage increased when the back pressures increased. Leakage rates were similar and acceptable.
Verification of Bernoulli Relationship	To determine if the Bernoulli Relationship may be used to non-invasively assess peak and mean pressure gradients	The Bernoulli relationship is adequate to non-invasively assess mean pressure gradients.
Flow Visualization	To qualitatively visualize the flow downstream	The flow accelerated through the valve and appeared to have a jet with a steep velocity gradient downstream. These results are as expected.
<p>Pulsatile hydrodynamic characterization [Non-circular config (oval)]</p> <p>Pulsatile pressure drop as a function of flow rate</p> <p>Total Regurgitant Volume as a function of Back Pressure</p>	<p>To provide pulsatile flow data for pressure drop, effective orifice area (EOA) and dynamic regurgitation performance</p> <p>Pulsatile Flow Leakage Volume vs. Backpressure tests were performed on valves with a circular diameter, then repeated with each compression</p>	<p>The Pulsatile Flow Pressure Drop test demonstrated differential pressure gradients that increased following the incremental compression of a valve. The highest pressure gradients occurred at a 33% original diameter reduction, and the largest gradient increase from previous compressions occurred between the interval of 25 – 33% diameter reduction.</p> <p>Regurgitation vs. Backpressure: the leakage volume slightly increased following each compression; however, the total regurgitant volume decreased as the valve was incrementally compressed due to a lower closing volume.</p>

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Test/Controls	Study Objectives	Results
<p>Valve in Valve</p> <p>The tests conducted were pulsatile hydrodynamic performance and an evaluation of migration in both a concentric and non-concentric configuration</p>	<p>To assess a second Melody device implanted within the initial Melody device</p>	<p>Test results were compared to data collected previously for a single Melody device deployed in a control, and indicated that valve in valve data is similar to data obtained for a single Melody device. The deployment of the second valve within the first valve did not alter the hydrodynamic performance.</p> <p>Migration: all dimensions fluctuated within the margin of error, <i>except for two measurements</i>. In those cases, the subsequent measurements fell within the margin or error. Measurements collected for the migration over time indicated that the measurements fluctuated within the margin of error similar to the "valve and valve" migration testing at five different back pressures. No data points were outside the margin of error, indicating that migration did not occur.</p>
<p>Migration vs pressure gradient</p>	<p>To measure the risk of migration in both the smallest and largest sizes</p>	<p>The maximum displacement seen for all devices tested was less than 1.40 mm at a pressure of 200 mmHg.</p>
<p>Migration of Concentric/ non-concentric device under sustained backpressure</p>	<p>To observe the potential migration of a non-concentric and concentric Melody valve within a failed bioprosthesis</p>	<p>Minimal, if any, migration of the Melody valves within the controls was seen. The largest migration of the samples evaluated showed an average maximum migration measurement of 165 ± 14.8 microns. Three valves in the study had no measurable migration over the eight week evaluation period.</p>
<p>Accelerated Wear Testing (AWT)</p>	<p>To assess long-term performance of the valve through accelerated wear</p>	<p>Test devices (Melody) were assessed versus control device (Hancock valved conduit). The results from this testing showed all Melody valves still functioning after 200 million cycles by holding a closed valve pressure in the test. Regurgitation increase of varying degrees was noted for all test valves with 5 of the 12 valves having regurgitation fraction values of 30% or higher at 200 million cycles, which would be considered moderate. Deployment size did not have an effect on regurgitation levels. Control devices (Hancock conduits) did not exhibit deterioration in function over the testing period.</p>
<p>Device Fatigue Testing</p>	<p>To assess the long-term durability of the stent component of the device</p>	<p>This test was performed to evaluate the worst-case loading condition that can be experienced by the stent as a result of compression between the chest wall and the beating heart (external compression loading). Testing was conducted by deploying stents within 18 mm silicone conduits with a 20 mm balloon, followed by compression cycling between flat plates to simulate external compression loading up to 100 million cycles. Test results showed in-vitro fractures rates that correlated with clinical fracture rates for patients subject to the worst-case loading condition.</p>

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Table 4 summarizes the *in vivo* preclinical testing performed (chronic sheep study).

Table 4: *In vivo* Test Summary (Chronic Sheep Study: 2005)

# Test/ Control Animals, Implant Duration	Study Objectives	Results
15 adult sheep [5 controls with 20mm Hancock LP Valved Conduit] [10 - 20mm Hancock LP Valved Conduit with 18mm Melody device] 5 months	To evaluate the healing characteristics in a chronic setting, and the general flow characteristics of the Melody device using fluoroscopy, pressure measurements, gross pathologic exam and histological analysis	Seven of the 10 test animals and 4 of the 5 control animals survived the 5-month implantation duration with no significant morbidity. Animal deaths were not device-related. All surviving animals in each group gained weight. These 11 animals remained clinically well and underwent sacrifice, and histopathological analysis per protocol.

X. Summary of Clinical Information

A prospective, non-randomized, multi-center evaluation was conducted at five centers in the United States to assess procedural success, safety, and short-term effectiveness of implantation of the TPV for RVOT conduit dysfunction.

The primary outcome measure for acute procedural success was the percentage of subjects attempted with an RV-PA gradient less than 35 mmHg post-implant, less than mild pulmonary regurgitation by angiography post-implant, and free of explant at 24 hours post-implant. The primary outcome measure for short-term effectiveness was the percentage of subjects with acceptable hemodynamic function at six months post-implant, where acceptable hemodynamic function was defined as mean RVOT gradient of ≤ 30 mmHg by CW Doppler, and a pulmonary regurgitant fraction of $< 20\%$ by MRI. Secondary outcome measures included NYHA, mean RVOT gradient, degree of pulmonary regurgitation by Doppler echocardiography, and the incidence of reoperation and reintervention.

The following clinical data are results from 99 subjects who were catheterized for potential implantation with the TPV from January 31, 2007 through December 12, 2008, with expected follow-up and adverse event data on these subjects current through March 27, 2009.

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Table 5: Baseline characteristics of the primary study population (N=99)

Variable/Category			
Weight (kgs)	61.8 ± 18.8	(99)	[60; 27 - 118]
Gender			
Male		63	(63.6%)
Female		36	(36.4%)
Age (Years)	20.6 ± 9.2	(99)	[18; 7 - 44]
Original Diagnosis			
Tetralogy of Fallot		52	(52.5%)
Transposition of the Great Arteries		10	(10.1%)
Truncus Arteriosus		8	(8.1%)
Aortic Valve Disease (Ross)		17	(17.2%)
Other		12	(12.1%)
RVOT Conduit Type			
Homograft		76	(76.8%)
Biologic Valved Conduit		12	(12.1%)
Non-valved Synthetic Conduit		6	(6.1%)
Bioprosthesis		3	(3.0%)
Other		2	(2.0%)
RVOT Conduit Size (mm)	20.5 ± 2.4	(99)	[20; 16 - 26]

Notes:

1. Data are presented as mean ± SD (n) [median; min - max] for continuous data, or number (%) of subjects for categorical data.
2. RVOT = Right Ventricular Outflow Tract

Table 6: Summary of primary outcome measures for procedural success and short-term effectiveness

Primary Outcome Measure	Results
Procedural Success	
Number of subjects catheterized	99
Number of subjects attempted	90
Number of subjects with procedural success	87
% of subjects with procedural success	96.7%
Short-Term Effectiveness	
# of subjects implanted with 6 months hemodynamic follow-up	64
# of subjects with acceptable hemodynamic function at 6 months	56
% of subjects with acceptable hemodynamic function at 6 months	87.5%

Notes:

1. Reasons for not attempting TPV implant were risk of coronary artery compression (n=4), RVOT not suitable for implantation (n=4), and need for concomitant procedures (n=1).
2. Three subjects did not meet all procedural success criteria: 1 had homograft rupture and was explanted within 24 hours, 1 had an RV-PA gradient >35 mmHg, and 1 had moderate pulmonary regurgitation by angiography.
3. All subjects met the short-term effectiveness criterion for valve competence; however, 6 subjects had mean RVOT gradients higher than 30 mmHg by Doppler echocardiography.
4. All hemodynamic data are from Core Imaging Lab.

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Table 7: Summary of NYHA functional class following TPV implant

NYHA Class	Six Months Post-Implant (N=71)		12 months Post-implant (N=35)	
	n	%	n	%
I	53	(74.6%)	26	(74.3%)
II	18	(25.4%)	9	(25.7%)
III	0	(0.0%)	0	(0.0%)
IV	0	(0.0%)	0	(0.0%)

Table 8: Mean RVOT gradient by CW Doppler following TPV implant

	Six Months Post-Implant (N=66)	12 months Post-implant (N=32)
Mean	20.3	22.3
SD	8.4	9.6
Min	7.3	9.5
Median	19.5	22.3
Max	51.8	48.3

Note:

1. Data are from Core Imaging Lab.

Table 9: Pulmonary Regurgitation by Doppler Echocardiography following TPV implant

Degree of Regurgitation	Six Months Post-Implant (N=65)		12 months Post-implant (N=32)	
	n	%	n	%
None	34	(52.3%)	14	(43.8%)
Trivial	27	(41.5%)	17	(53.1%)
Mild	4	(6.2%)	1	(3.1%)
Moderate	0	(0.0%)	0	(0.0%)
Severe	0	(0.0%)	0	(0.0%)

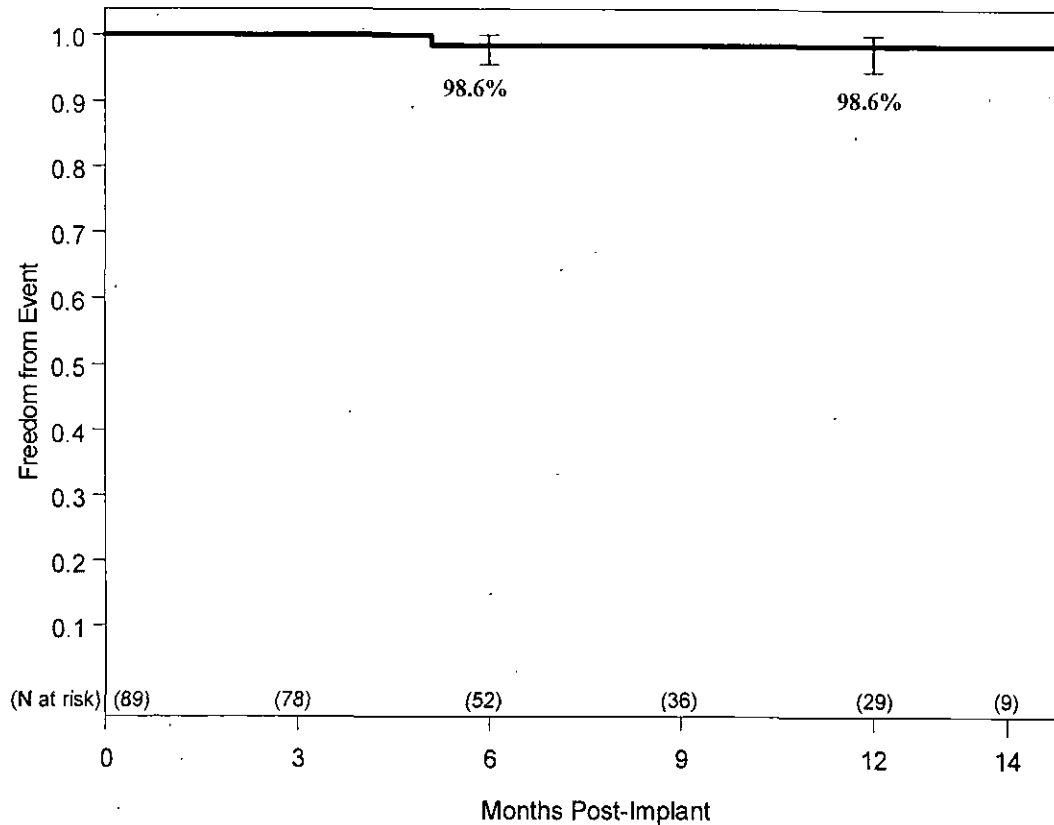
Note:

1. Data are from Core Imaging Lab.

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Figure 4: Freedom from Reoperation



Notes:

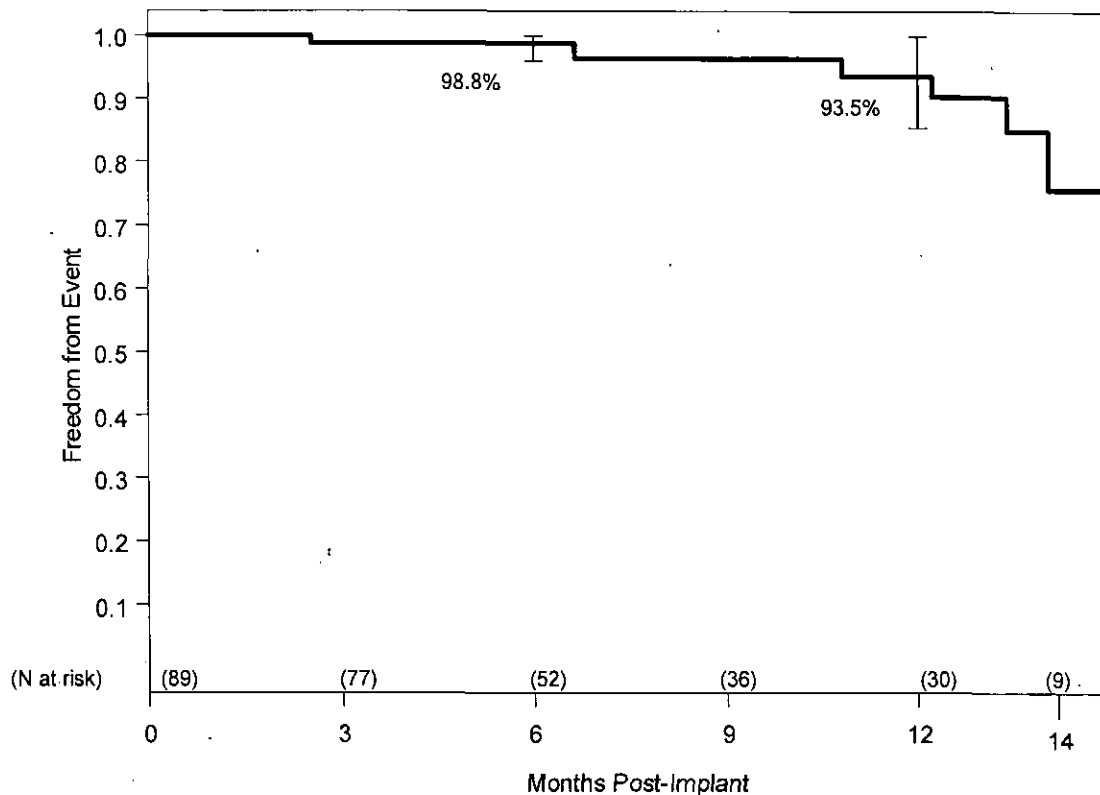
1. One subject had reoperation (conduit exchange) at 5 months for recurrent obstruction associated with stent fracture.
2. The error bars are the 95% confidence interval at 6 month and 12 months, respectively.
3. Freedom from reoperation (conduit exchange) was 98.6% (SE = 1.6%), 98.6% (SE = 2.2%), at 6 months and 12 months respectively

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Figure 5: Freedom from Reintervention

Reintervention is defined as balloon angioplasty or implantation of an additional Melody TPV



Notes:

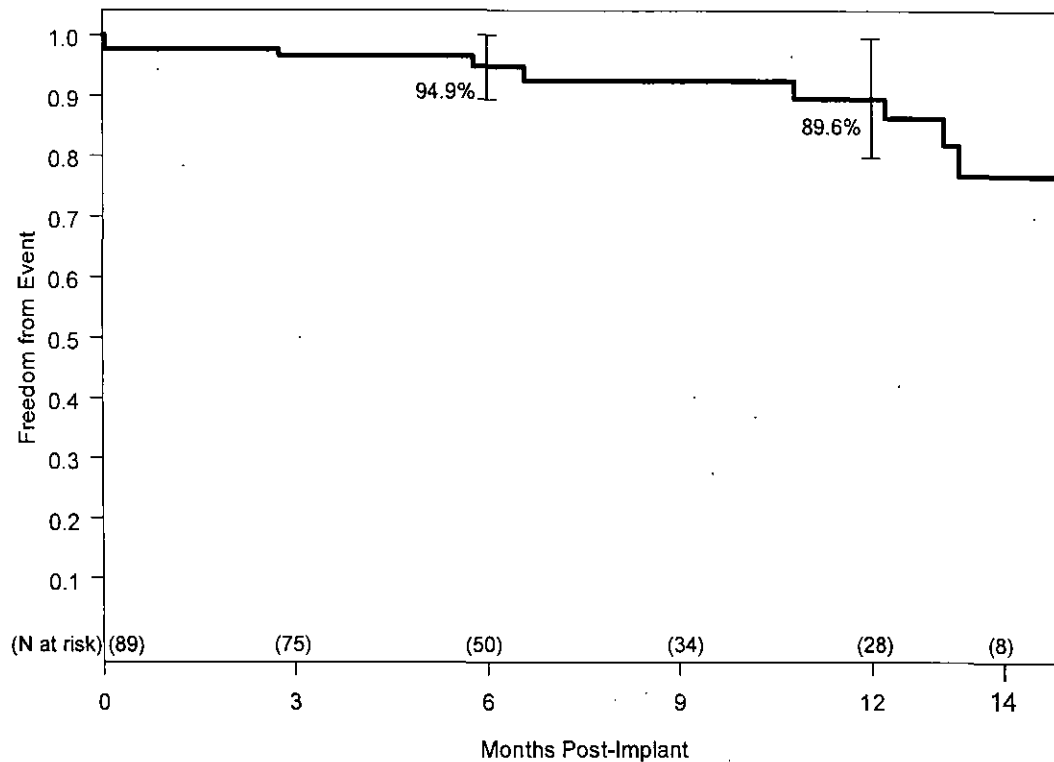
1. Reinterventions were balloon angioplasty in one subject, and repeat implantation of a second TPV in 5 subjects.
2. The error bars are the 95% confidence interval at 6 months and 12 months, respectively.
3. Freedom from re-intervention was 98.8 % (SE =1.5%), 93.5% (SE = 4.3%), at 6 months and 12 months, respectively.

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Figure 6: Freedom from TPV Dysfunction (Composite)

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 greater than 40 mmHg).



Notes:

1. The error bars are the 95% confidence interval at 6 months and 12 months, respectively.
2. Freedom from TPV dysfunction was 94.9% (SE = 3.0%) at 6 months, and 89.6% (SE = 5.5%) at 12 months

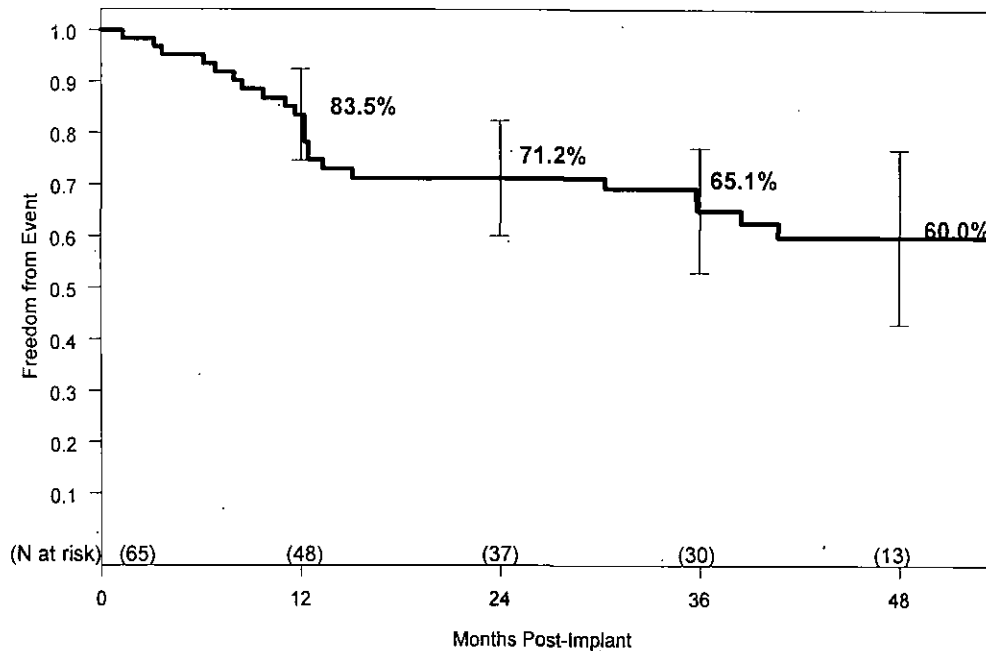
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Outside the United States (OUS) Cohort

In addition to the data from the US IDE trial, clinical data was also available on a 68 subject cohort from Professor Philipp Bonhoeffer's experience outside of the United States. These subjects were implanted between 2003 and 2005, with follow-up current through March 27, 2009. Data from that cohort is provided below.

Figure 7: Freedom from Stent Fracture (OUS)



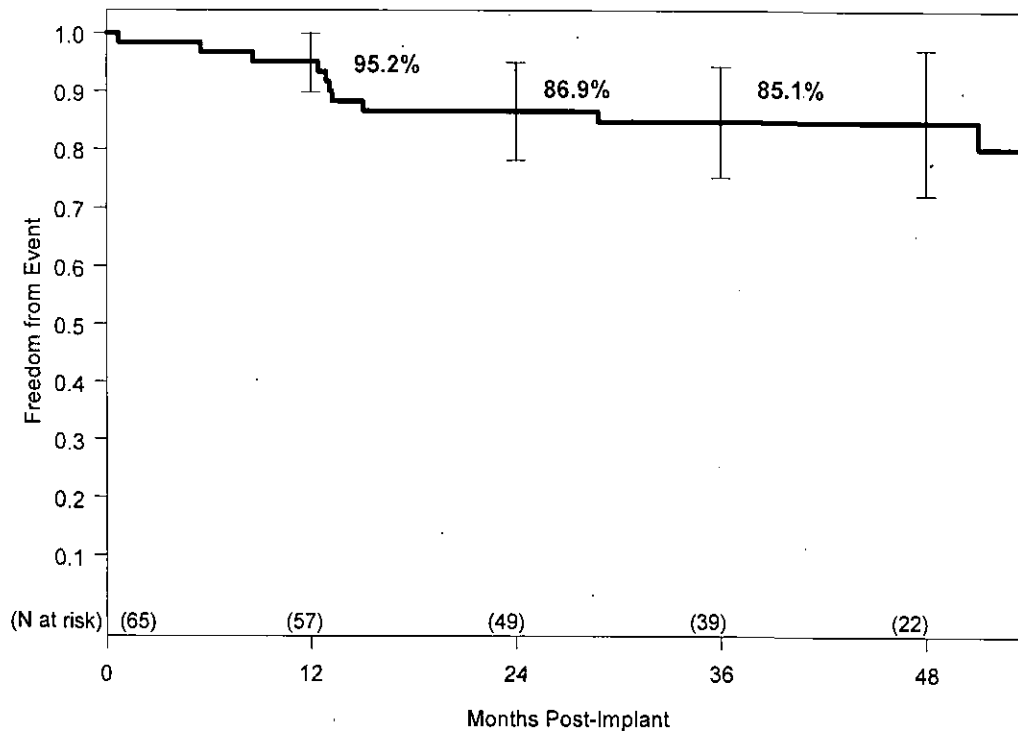
Note:

The error bars are the 95% confidence intervals at each annual interval.

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Figure 8: Freedom from Surgical Conduit Replacement (OUS)

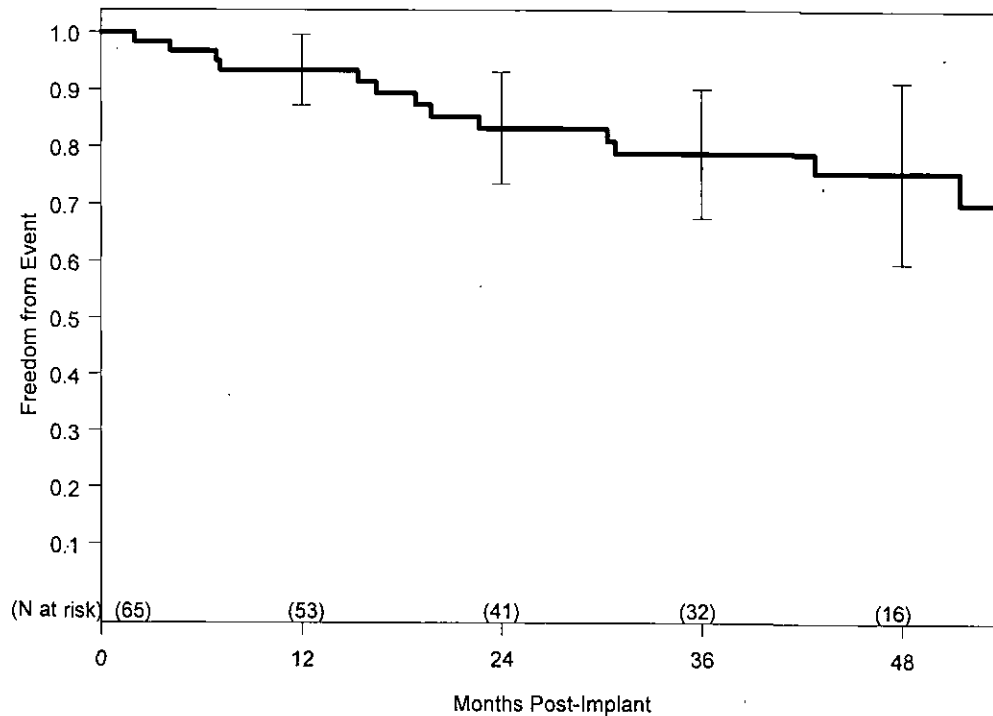


Note:
The error bars are the 95% confidence intervals at each annual interval.

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Figure 9: Freedom from Repeat Implantation of Another TPV (OUS)



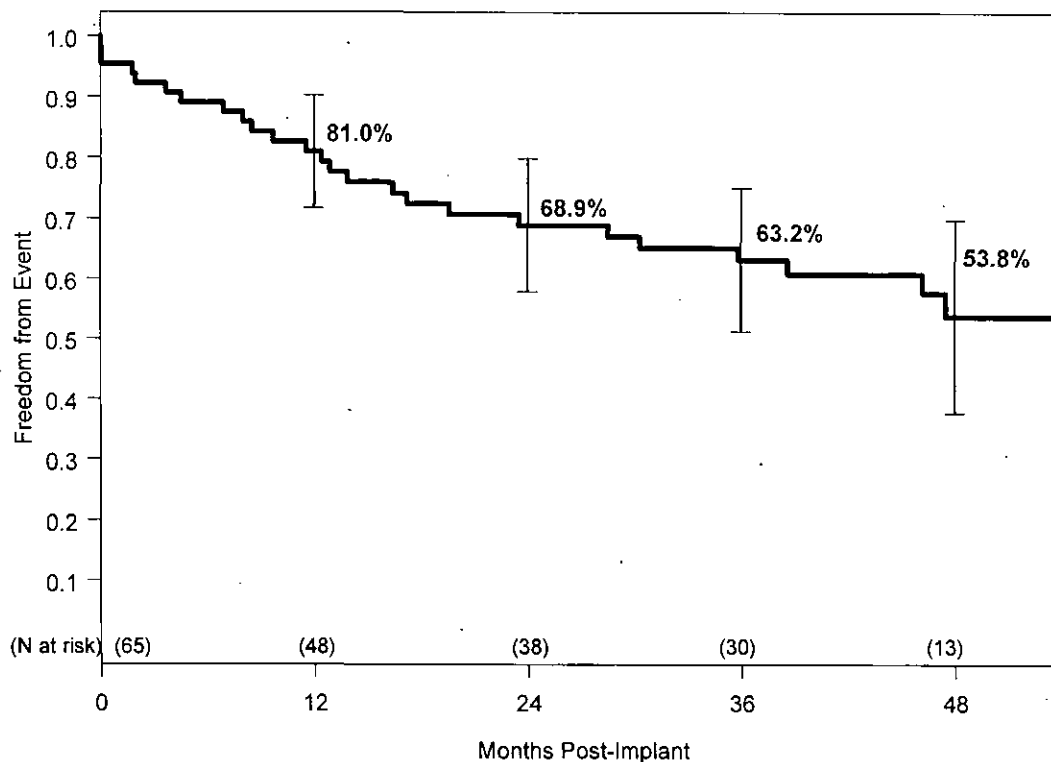
Note:
The error bars are the 95% confidence intervals at each annual interval.

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Figure 10: Freedom from TPV Dysfunction (OUS)

TPV dysfunction is a composite outcome, defined as RVOT reoperation for recurrent conduit dysfunction or device-related reasons, implantation of a second TPV, or hemodynamic dysfunction of the TPV (moderate or greater pulmonary regurgitation, and/or a maximum instantaneous gradient of 50 mmHg or higher).



Note:

The error bars are the 95% confidence intervals at each annual interval.

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XI. Risk/Probable Benefit Analysis

The Melody device is designed for transcatheter implantation via the Ensemble delivery system into an existing conduit in a right ventricular outflow tract (RVOT) that has become dysfunctional. Therefore, this patient population has already undergone at least one surgery for their congenital condition(s), and will need to undergo additional procedures in order to maintain optimum cardiac function.

Since there is no permanent surgical "cure" for most of the congenital anomalies involving the RVOT, patients face a lifetime of continued intervention. Most patients require procedures after successful repair for many reasons, including: residual defects, complications, the development of long-term sequelae, conduit performance issues, or degeneration.

Because the current best treatment modes for RVOT reconstruction will eventually fail, and the indications for and the timing of the reintervention remain unclear, a clear need for improvement in conduit performance via a less invasive method is warranted. The goal is to improve the quality of patient long-term survival by lifetime patient management. To this end, the transcatheter deployment of the Melody device aims to reduce the number of surgeries required over a lifetime by this patient population.

The intended role of the Melody Transcatheter Pulmonary Valve is to restore pulmonary valve function in patients with a dysfunctional RVOT conduit and a clinical indication for pulmonary valve replacement. Unlike currently available options for pulmonary valve replacement, the TPV is intended to be placed with a transcatheter delivery system, and thus does not require surgical incisions, open heart surgery, cardiopulmonary bypass, or the various morbidities associated with surgical pulmonary valve replacement. The ultimate goals and durability of the TPV may differ among patients with different indications. At a minimum, the intention is that the TPV will improve the hemodynamic function of the existing conduit, mitigate the adverse impact of pulmonary regurgitation and/or RVOT obstruction on the RV, and effectively extend the longevity of the existing conduit and defer the need for conduit replacement. In some patients, delaying surgical conduit re-intervention may reduce the number of open heart surgeries required over the course of their lifetime, thereby decreasing the cumulative morbidity and risk associated with such operations.

Safety Assessment

Clinical evidence has been gathered from the clinical experience of Professor Philipp Bonhoeffer, as well as the clinical data from the 99 US IDE subjects. Professor Bonhoeffer's initial experience demonstrated that transcatheter implantation of the Melody device could be accomplished with a high degree of

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procedural success, and that the incidence of device-related morbidity in follow-up was acceptable. In support of Professor Bonhoeffer's experience, the US IDE study similarly showed a high degree of procedural success and a low incidence of procedure-related complications, demonstrating that the transcatheter implantation can be performed safely, with easily transferrable clinician skills. The collective data indicate a low procedural and device-related mortality, and a relatively low number of device-related adverse events.

Probable Benefit Assessment

The findings of the US IDE study indicate that the Melody device probably improves pulmonary valve competence. The Melody device acutely reduced pulmonary regurgitation to trivial or none in all patients, sustained at one year. At one year, the majority of patients had no pulmonary regurgitation, and all had mild or less. The improvement in pulmonary valve competence after Melody implantation is reflected in significant reduction of RV end-diastolic volume. Absolute and indexed (body surface area) RV end-diastolic volumes fell by approximately 20%. Additionally, although relief of RVOT obstruction is not the primary purpose of the Melody device, it frequently coexists in this patient population and, therefore, is an important consideration in assessing the probable benefit of the device. Professor Bonhoeffer's experience demonstrated that the Melody device provides acceptable relief of RVOT obstruction in the majority of patients, as well as a high degree of pulmonary valve competence over the follow-up period. In the US IDE study, Melody implantation resulted in a significant decrease in the directly measured RV-PA gradient, RV pressure, and RV:aortic pressure ratio. The collective evidence supports the claim of probable benefit as a treatment for RVOT conduit regurgitation and stenosis over the mid-term, both prolonging the functional life of previously implanted RVOT conduits, and improving subjective and objective indices of clinical status in this patient population.

XII. Panel Recommendation

At an advisory meeting held on July 22, 2009, the Circulatory System Devices Advisory Committee Panel recommended that Medtronic's HDE for the Melody/Ensemble System be approved with conditions.

XIII. CDRH Recommendation/Decision

CDRH has determined that, based on the data submitted in the HDE, that the Medtronic Melody® Transcatheter Pulmonary Valve (Model PB10) and Medtronic Ensemble® Transcatheter Valve Delivery System (Model NU10) will not expose patients to an unreasonable or significant risk or illness or injury, and the probable benefit to health from using the device outweighs

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the risks of illness or injury, and issued an approval order on January 25, 2010.

XIV. Approval Specifications