FDA Executive Summary

Prepared for the
September 11, 2012 meeting of the
FDA's Pediatric Advisory Committee

H080002

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

August 9, 2012

INTRODUCTION

In accordance with the Pediatric Research Equity Act, this review provides a safety update based on the post-marketing experience with the use of the Medtronic Melody® Transcatheter Pulmonary Valve (TPV) and Medtronic Ensemble® Transcatheter Valve Delivery System in pediatric (weight ≥30 kg through age 21 years) and adult patients since approval. The Medtronic Melody® TPV is a percutaneously delivered pulmonary heart valve replacement for pediatric and adult patients. It was approved in January, 2010 by the Center for Devices and Radiological Health under Humanitarian Device Exemption (HDE) application H080002.

The purpose of this review is to provide the Pediatric Advisory Committee with post-marketing safety data so the committee can advise the Food and Drug Administration (FDA) on potential safety concerns associated with the use of this device in children. This memorandum will include summaries of the pre-market clinical study, postmarket medical device reporting (MDR) for adverse events, post-approval studies, and the peer-reviewed literature associated with the device. As an annual safety review for this device was undertaken by this panel in September of 2011, each postmarket section will briefly summarize last year's presentation, followed by additional information gained in the interim year.

At the conclusion of the 2011 presentation, 14 committee members concurred with returning the device to routine MDR and literature review and that the product should return to the committee after the post-approval studies are completed. Three (3) committee members did not concur. Seventeen (17) committee members unanimously agreed that the exemption on the limit for profit making remains appropriate at this time. More detailed information regarding the 2011 presentation can be found at CDRH Safety Review of the Medtronic melody Transcatheter Pulmonary Valve (TPV) and Ensemble Transcatheter Valve Delivery System (PDF - 484KB)

At this year's panel meeting, the Agency will once again ask for your recommendations regarding the need for continued monitoring of safety and the appropriateness of the profit-making exemption.

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:

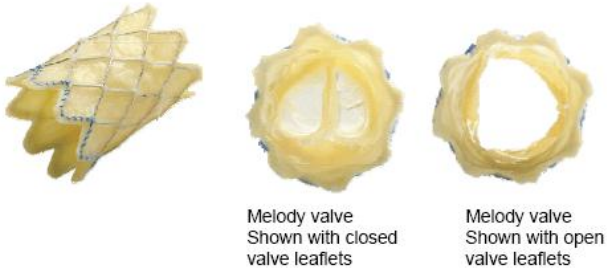
- Existence of a full (circumferential) RVOT conduit that was equal to or greater than 16 mm in diameter when originally implanted and
- Dysfunctional Right Ventricular Outflow Tract (RVOT) conduits with a clinical indication for intervention, and either:
    - Regurgitation: ≥ moderate regurgitation, or
    - Stenosis: mean RVOT gradient ≥ 35 mmHg.

BRIEF DEVICE DESCRIPTION

The device implant system consists of two components:

- The Medtronic Melody® Transcatheter Pulmonary Valve consists of a heterologous (bovine) jugular valve sutured within a laser-welded platinum-iridium stent with gold brazing of the welds. Pulmonic Sizes: 18, 20, and 22mm. Stent length: 28mm.

Figure C1: Melody Transcatheter Pulmonary Valve



- The Ensemble® Transcatheter Valve Delivery System consists of a balloon-in-balloon catheter with a retractable polytetrafluoroethylene (PTFE) sheath and distal cup large enough to front-load the stented valve after crimping. The delivery system has a 22 Fr crossing profile. At inflation, the inner balloon is half the diameter of the outer balloon. Both balloons are made of nylon. The delivery system comes in outer balloon sizes of 18, 20, and 22 mm. The catheter's sheath has a side-port used to flush the system and a hemostatic sleeve over the sheath to minimize bleeding at the insertio mpatible with a 0.035-in guidewire.

Figure C2: Ensemble Transcatheter Valve Delivery System

Hereafter, the device and delivery system will be referred to collectively as the "Melody® TPV" or "TPV."

REGULATORY HISTORY

The Melody TPV was granted Humanitarian Use Device designation on July 10, 2007 by FDA's Office of Orphan Products Development. Medtronic conducted a clinical study of the Melody® TPV in support of their HDE application, and submitted results to FDA in August 2008. The July 2009, FDA Circulatory System Devices Advisory Panel voted 12-0 that the HDE was "approvable with conditions" and the device was approved on January 25, 2010. As a condition of approval, the sponsor was requested to conduct two post-approval studies (PAS) – one being for the long term follow-up of the IDE patients and the second to evaluate device safety and effectiveness in a representative population of providers.

PREMARKET DATA: THE IDE CLINICAL STUDY

The Melody® TPV clinical study was a prospective, non-randomized trial assessing the use of the Melody® TPV in patients with dysfunctional right ventricular outflow tract (RVOT) conduits and a clinical indication for intervention.

Enrollment Criteria

Inclusion Criteria

- Weight greater than or equal to 30 kilograms;
- Full RVOT conduit $\geq$ 16 mm in diameter when implanted, or stented bioprosthesis with a rigid sewing ring in the RVOT with internal diameter $\geq$18 mm and $\leq$ 22 mm

For patients in NYHA Classification II, III, or IV:

- Moderate (3+) or severe (4+) pulmonary regurgitation; or
- Mean RVOT gradient greater than or equal to 35 mmHg.

For patients in NYHA Classification I:

- Severe pulmonary regurgitation with RV dilatation or dysfunction;** or
- Mean RVOT gradient greater than or equal to 40 mmHg.

Exclusion Criteria

- Major/progressive non-cardiac disease with a life expectancy of less than one year; or
- Obstruction of the central veins such that the delivery system cannot be advanced

Study Endpoints

Primary Outcome Measures

Safety (6 month time point)

- % subjects with procedure or device-related mortality
- % subjects that experience serious procedure or device-related AE.

Effectiveness

- % of successful attempts to implant the device
- % subjects with acceptable hemodynamic function at six months (mean RVOT gradient $\leq$ 30 mmHg and Pulmonary regurgitant fraction < 20%)

Secondary Outcome Measures

Safety:

- Incidence of device-related adverse events over the six month follow-up
- Incidence of explant or re-intervention on the Melody® TPV

Effectiveness (at 6 months) included

- Degree of pulmonary regurgitation by echocardiography;
- Mean RVOT gradient by echocardiography;
- New York Heart Association (NYHA) functional class;

Success Criteria

The following were proposed by the sponsor and accepted by FDA as being appropriate for allowing a determination of safety and probable benefit:

- 95% subjects are free from device/procedure-related mortality at 6 mo;
- <30% subjects will experience a serious device or procedure-related AE over 6 mo;
- > 80% of attempts to implant the Melody® TPV will be successful; and
- >75% subjects will have acceptable hemodynamic function at 6-month

Patient Enrollment

A total of 99 patients (including 65 pediatric subjects) underwent cardiac catheterization and thus were enrolled in the study; these patients constituted Safety analysis subset. Nine (9) patients did not have implantation attempted, therefore 90 patients (including 60 pediatric subjects) constituted the Procedural Success subset. One of the implanted patients suffered an intra-procedural homograft rupture necessitating TPV removal. Therefore, 89 patients were followed for the effectiveness evaluation. The average age of enrolled subjects was 20.6 with a range of 7-44.

Study Results – Safety

Primary Safety Outcomes

Mortality

There was one device- or procedure-related death by 6 months in an adult subject (coronary dissection during implantation angiogram, requiring ECMO support, and died from an intracranial hemorrhage on post-procedure day 20). The mortality rate met the primary safety success criterion.

Morbidity

Serious Adverse Event (SAE) Rate related to the device or procedure was 5.1% including 4 four procedure-related events (homograft rupture, branch pulmonary artery rupture, supra-ventricular tachycardia, and coronary dissection) and one device-related SAE (stent fracture that necessitated repeat TPV placement). The rate among the pediatric group was 4.6%.

Secondary Safety Outcomes

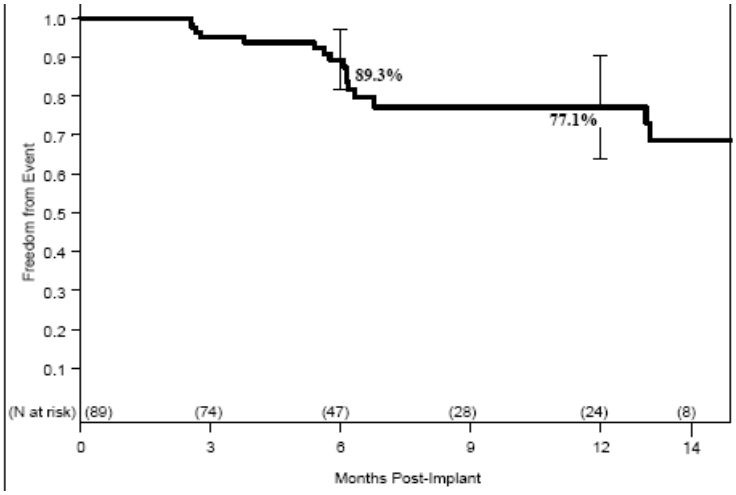
No TPV embolization, thrombosis, endocarditis or pulmonary thromboemboli occurred. Coronary artery compression by the Melody® TPV did not occur, although 4% of enrolled patients had the implantation aborted due to investigator concern for causing this event. There was one event of RVOT conduit rupture. The table and sections below provide additional details regarding the adverse events seen in the IDE trial.

Event	Subjects with Event	
	N	(%)
Embolization of the TPV	0	(0.0%)
Stent fracture (All)	16	(18.0%)
Minor stent fracture	11	(12.4%)
Major stent fracture	5	(5.6%)
Structural deterioration of the TPV	0	(0.0%)
Paravalvular leak	0	(0.0%)
Thrombosis of the TPV	0	(0.0%)
Pulmonary thromboembolism	0	(0.0%)
Endocarditis	0	(0.0%)
Hemorrhage	0	(0.0%)
Valve dysfunction: stenosis	6	(6.7%)
Worsening of tricuspid regurgitation associated with right heart failure	1	(1.1%)
Non-structural dysfunction	0	(0.0%)
Re-intervention on the TPV	6	(6.7%)
Reoperation (conduit exchange)	1	(1.1%)

Note:
Subject 1066 had valve dysfunction (stenosis) that presented as worsening of tricuspid regurgitation associated with right heart failure.

Stent Fracture

Stent fracture was observed in 16 of 89 evaluable patients. One fracture was classified as "major" (e.g., required intervention) at 3 mo while the remaining were "minor" at identification and at 6 months; however, 4 of these 15 minor fractures progressed to "major" fractures between 7 and 14 months after implantation.



Re-intervention

All 5 "major" fractures underwent valve-in-valve re-implantations with another TPV. All cases had evidence of RVOT obstruction with RV hypertension. One patient required reintervention for RVOT obstruction that was not associated with an identified stent fracture; this patient was treated with balloon angioplasty.

Reoperation

There was one surgical conduit replacement procedure performed in a subject who had undergone a second TPV implantation at 3 months' follow-up and then surgical conduit exchange 2 months after the second Melody® TPV was implanted.

Study Results - Effectiveness

Primary Effectiveness Outcomes

Procedural Success

Eighty-seven of the 90 (96.7%) implanted patients met the criteria for procedural success. One patient required explant due to homograft rupture, another patient failed because the post-implantation gradient was >35 mmHg, and a third had moderate regurgitation. All three failures were in adult subjects.

Effectiveness

Acceptable hemodynamic function was achieved in 87.5% of implanted subjects at 6-months (84.4% in pediatric group). In all 8 cases of failure, the reason was mean RVOT gradient >30mmHg. Two of the 8 underwent repeat TPV placement, and a third patient underwent balloon angioplasty.

Secondary Effectiveness Endpoints (at 6 months)

The percentage of patients who completed the various 6-month secondary effectiveness assessments by the lock date was between 57% and 80%.

- RVEDV and pulmonary regurgitant fraction were statistically decreased at 6 months.
- Pulmonary regurgitation for the majority of patients was trace or none at 6 months
- Average RVOT gradient at 6 and 12 months remained below pre-implantation value of 31.4mmHg. The difference at 6 months was statistically significant.
- Most were at Class I at 6 months and 12 months.

PREMARKET DATA: PROFESSOR BONHOEFFER U.K. DATA

Longer-term results provided to FDA at the time of the Melody HDE application were based Professor Bonhoeffer's series in the UK of 68 sequential patients implanted from 2003-2005. The duration of follow-up was 3-5 years. The UK and US cohorts differed at enrollment mainly in terms of heart failure symptomatology (42% vs 17%) and proportion of patients with a mixed PR/PS indication for the Melody® TPV (40% vs 20%).

Stent fracture was identified in 22/65 implanted patients. Thirteen required re-intervention or reoperation including explantation of embolized Melody® TPV (1); second valve-in-valve Melody® TPV implantation (8); and operative conduit exchange because of fracture-associated RVOT obstruction (4). Recurrent RVOT obstruction developed in 18/65 patients, at a median time of 18 months post-implantation; patients having stent fractures accounted for 13/18 of the recurrent RVOT obstruction group. Three patients developed endocarditis.

Surgical re-intervention was required in 10 patients due to embolization, fracture-associated RVOT obstruction, residual valve stenosis, and endocarditis.

POSTMARKET DATA: ANNUAL DISTRIBUTION NUMBER

The Pediatric Medical Device Safety and Improvement Act of 2007 amended section 520(m) of the Food and Drug Administration Amendments Act and now allows HDEs indicated for pediatric use and approved on or after September 27, 2007, to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). The ADN is the number of individuals affected by the disease or condition per year (i.e., annual incidence) multiplied by the number of devices reasonably necessary to treat an individual. The ADN cannot exceed 3,999, if the calculated ADN exceeds 3,999 – FDA must restrict to the ADN to 3,999 based upon FDAAA legislation

The ADN for Melody was 2996 when it was approved by CDRH. The ADN was restricted to 2996 because at the time of HUD designation, the annual incidence was 2996 and the number of devices needed to treat an individual is one (1). In 2010 there were a total of 524 Melody TPVs sold in the U.S. In 2011, 719 Melody valves were sold in the U.S. Of these, 548 were implanted and 314 were implanted in pediatric patients.

As stated in section 520(m)(8) of the Act, the agency's Pediatric Advisory Committee will annually review all HUDs intended for use in pediatric patients that are approved on or after September 27, 2007, to ensure that the HDE remains appropriate for the pediatric populations for which it is granted.

POSTMARKET DATA: MEDICAL DEVICE REPORTS (MDRs)

MDR Data Presented to PAC in 2011

From approval through July 1, 2011, FDA received 32 MDRs for the TPV and age was provided in 18. Nine (9) MDRs cited events in the pediatric population (≤ 21) patients. The 9 pediatric patients ranged from 8-19 years with an average of 15 years. The following information relates to the 32 reports-note is made when involving a pediatric subject.

Peri-procedural Events (Occurring within the 1st 24 hours of implantation), (N=7)

Left Coronary Artery (LCA) Compression (n=1 total, n = 0 pediatric)

Post-implant chest pain and elevated troponin levels. Catheterization revealed partial LAD compression caused by the proximal part of the pre-stent.

Pseudo-aneurysm contained rupture (n=1 total, n=0 pediatric)

Two covered stents were placed within TPV to decrease filling of the pseudo-aneurysm.

Ventricular Septal Defect (VSD) size increased (n=1 total, n=0 pediatric)

Patient required surgical closure of the VSD and a revision of the conduit with TPV removal.

TPV deployed in Right Ventricle (RV) (n=2 total, n=2 pediatric)

The TPVs were unsheathed inadvertently or prematurely and deployed in RV.

Difficult deployment/papillary muscle tear/regurgitation (n=1 total, n=0 pediatric)
Tear in TV papillary muscle during deployment with muscle encroaching on RVOT.

Inappropriate device size (n=1 total, n=0 pediatric)
Surgeon indicated the TPV was too small for the patient, resulting in explant.

All 7 patients with peri-procedural events required intervention(s) including

- device explant (in 4 patients)
- 2nd TPV (valve-in-valve) implant (1)
- additional stent (2) or covered stent (1),
- VSD surgical repair (1) and
- surgery using endoscopic equipment (1).

Several patients with peri-procedural events required more than one intervention.

With respect to the two pediatric subjects who experienced premature TPV deployment within the right ventricle, one subject underwent surgical intervention to reposition the device, and the other underwent additional stenting.

Post-implant events (after 24 hours post implant), (N=25 total, N=7 pediatric)
Endocarditis (n=1 total, n=0 pediatric)
Cultures positive for Enterococcus but TEE negative; however, patient given antibiotics.

Stenosis without Stent Fracture (n=2 total, n=0 pediatric)
In one patient, an Echo exhibited valve stenosis with elevated gradient (28 mmHg) at 12 months. There was severe valve regurgitation after balloon angioplasty and the patient required a 2nd Melody TPV implant. The other patient had stenosis possibly related to pre-existing endocarditis and required a 2nd Melody TPV implant 7 months post TPV implant.

Stent Fracture (n=22 total, n=7 pediatric)
The time to diagnosis of fracture was 3-37 months. Twelve of the MDRs indicated patients were asymptomatic, no loss of stent integrity, or no intervention(s) required. The fracture was usually identified on routine imaging. The remaining fractures required interventions. The following are the findings/symptoms reported in the MDRs where listed.

- "Gradient" (reported in 8 MDRs)
- TPV compressed/oval configuration- (5),
- RVOT (Right Ventricular Outflow Track) obstruction (2),
- Embolization of stent strut to pulmonary artery (2),
- Stenosis (1)
- Increased fatigue with exertion (1)
- Chest pain (1).

Fracture progression was described in 6 MDRs (including 4 pediatric subjects age 8-18) where stent fracture was noted at an early time without signs and symptoms, but progressed to other findings months to years later. Five of these reports indicated an intervention was eventually required, including in 3 of the 4 pediatric cases (explant in 2, and angioplasty in 1).

The table below provides additional details on the fracture cases. Shaded rows represent pediatric subjects.

Age (yrs)	Sex	Fracture Identified	Subsequent Event Time	S & S*, Findings	Intervention(s)
Stent fracture required intervention, n=10					
18	M	3 mos	21 mos	Stenosis	Explant
9	M	6 mos	7 mos	Chest pain; gradient 20mmHg; TPV compression front to back: oval shape	Angioplasty
*	F	3 mos	6 mos	Gradient 19 mmHg	2nd TPV
*	*	6 mos	36 mos	1 fx* at 6 mons progressed to 5 fxs at 24 mons; gradient 35 mmHg	2 stents and 2nd TPV
8	M	6 mos	36 mos	1 fx at 6 mons progressed to 7 fxs, RVOT obstruction, increased gradient	Explant
19	M	3 mos		RVOT obstruction	Explant
18	F	31 mos		fx noted post ballooning, high gradient	Angioplasty, Stent, 2nd TPV
*	*	12 mos		No information	2nd TPV
*	*	27 mos		Stent embolization in pulmonary artery	Strut retrieved, Stents & 2nd TPV
*	*	32 mos		Strut embolization (lung), increased gradient	Stent and 2nd TPV
Stent fracture, no intervention required, n=12					
27	M	4 mos		No AE* reported	No
26	M	4 mos		No AE reported	No
33	F	24 mos		No AE reported	No
14	M	3 mos	12 mos	No AE reported, fx at 3 month, multiple strut fx at 1 yr, gradient 40mmHg	No
16	M	6 mos		No AE reported, stent fx at 6 mons, AP dimensions were diminished to 10-13 mm. Stent appeared to be stable.	No
*	M	6 mos		No AE reported. Gradient 20mmHg	No
*	F	24 mos		No AE reported	No
*	*	25 mos		No AE reported	No
24	M	37 mos		No AE reported	No
*	*	25 mos		No AE reported	No
*	F	24 mos		No AE reported	No
33	M	24 mos		No AE reported	No

* S & S: signs and symptoms; ** fx: fracture; *** AE: Adverse effects

Intervention Required for Stent Fracture

All 5 adults with fracture did not have any adverse effects and did not require any intervention(s), whereas 5 of 7 pediatric patients with the same problem required additional interventions including device explant (3), angioplasty (1) and 2nd TPV implant (1).

MDRs Received From July 2011 – July 2012 (New Information)

Since the September 2011 Pediatric Advisory Committee meeting, and through July 1, 2012, an additional 42 unique MDRs have been received by FDA for the device. Patient age information is available in 31 of the MDRs. Of these, 17 reports included pediatric (≤ 21) patients, ranging in age from 7-20 years.

MDRs included 3 reports associated with patient death including pulmonary artery occlusion with stent fracture in 2 adult patients and endocarditis in a pediatric patient. Please note that the causal relationships between the reported problems and the 3 deaths have not been confirmed.

Peri-procedural events (within 24 hours post implant) (N=5 total, n=2 pediatric)

Left Coronary Artery (LCA) Occlusion (n=3 total, n=1 pediatric)

A total of 3 MDRs cited this adverse event. These included 1 pediatric case where there was an occlusion in LCA following balloon dilation. The TPV was removed and a homograft was implanted.

Pulmonary Artery Occlusion (n=2 total, n=1 pediatric)

A total of 2 MDRs were received including one pediatric case where after conduit pre-stenting and TPV implant, follow up angiograms showed possible right pulmonary artery occlusion. The patient had a surgery for TPV removal and conduit revision. The non-pediatric case was associated with patient death.

Post-implant events (after 24 hours post implant) (N=37 total, n=15 pediatric)

Stent Fracture (n=16 total; n=6 pediatric)

In the past year, stent fracture continued to be the most frequent event reported in MDRs - seen in 16 of the 42 MDRs received. Fractures were diagnosed from 3-49 months after implantation (mean 16 months). Nine of the 16 stent fracture MDRs reported no adverse patient effects and no interventions or actions were required. The remaining 7 patients required interventions such as valvuloplasty, stenting, additional Melody TPV (valve-in-valve) implantation or TPV explant.

Stent fracture progression was noted in 4 cases where fracture was observed at an early time without signs and symptoms, but progressed to others findings 9 months to 3 years later and subsequently required interventions. One of these 4 cases involved a 16 year old (see below). One (non-pediatric) case was associated with a patient death.

Six of the 16 MDRs cited stent fractures in **pediatric** populations. Within this group, the time from implant to diagnosis of fracture was 6-28 months (mean 14 months). The table below provides additional detail on the 6 pediatric subjects with stent fracture.

Age	Gender	TTEO (months)	Reported problem	S & S*, Findings	Interventions
No interventions required, n=4					
7	F	17	Multiple stent fxs*	No AE*	No
11	M	18	A type 1 stent fx	Mild regurgitation, moderate obstruction of TPV	No
13	M	6	A minor stent fx	No AE	No
18	M	28	3 stent fxs	No AE	No
Intervention(s) required, n=2					
15	M	7	Stent fx		Stenting & 2nd TPV
16*	M	0	Dilation could not be achieved	Gradient 32 mmHg at discharge	No
		8	No stent fx	Gradient 70 mmHg, Peak-to-peak gradient 40 mmHg	Balloon dilatation to 6 atm
		8	Longitudinal fxs post dilatation, TPV collapsed		Stenting & 2nd TPV
		44	Stenosis of both TPVs, Stent fx and kinking during dilatation	Mean Gradient 34 mmHg, Max Gradient 62 mmHg.	Balloon dilatation, resulting balloon ruptured.
		44	Balloon ruptured	Gradient 20-25 mmHg	Snare ruptured balloon.

*S & S: Signs and symptoms; * Fxs: Facture(s); *AE: Adverse effects; *ATM: Atmosphere

**This subject had multiple events/interventions over 44 months.*

Stenosis (n = 11 total; n=3 pediatric)

Stenosis was reported in 11 MDRs. The 3 pediatric cases included

- An 11 year-old male who underwent balloon dilation at 40 months post-implant for an asymptomatic high gradient stenosis. No adverse effects were reported.
- A 17 year-old female who had the valve explanted 6 months after implantation secondary to leaflet thickening/stenosis, high gradients, and insufficiency. At surgery a large infected false aneurysm was noted, although there was no evidence that the Melody valve was obstructed or infected
- A 10 year-old female underwent valve explant after 16 months due to increased gradients and decreased RV function. On explant the valve was stenosed, calcified.

Valve insufficiency/regurgitation (n=3 total, n=2 pediatric)

Three reports citing this event were received. Two of these were pediatric cases including:

- A 20 year old male who had the valve explanted/replaced due to mild-moderate pulmonary insufficiency secondary to a dysfunctional leaflet
- A 12 year old male underwent valvuloplasty 1 year post-implant due to high gradient. The patient had positive cultures for S. viridans and was treated with antibiotics.

Endocarditis/Infection (n=2 total, n=2 pediatric)
Both cases of endocarditis were pediatric subjects, and one was associated with a death.

- A 19 year old male with a prior history of SBE presented 2 years post-implant with high gradients and suspected SBE, with renal failure and the need for a RV assist device. Attempts at balloon dilation resulted in stent fracture and explantation of the device. The patient **expired** 40 days after the TPV explant from multisystem organ failure due to shock from *S.aureus* endocarditis.
- A 19 year old male presented with fever and positive *S. epidermidis* cultures 3 weeks post implant. No vegetations were seen on Echo and he was treated with antibiotics. The patient continued to have severe RV dysfunction/hypertrophy, moderate tricuspid regurgitation and hypertrophy along with conduit obstruction. Six months post implant, the TPV was explanted. There were no reported Melody dysfunctions found.

Valve compression (n= 1 total, n=1 pediatric)
This was in an 18 year old female who developed significant regurgitation 9 months after implant. On catheterization the proximal end of the TPV appeared compressed and the gradient was 35 mmHg. The TPV was re-dilated. Upon balloon inflation, at least two stent fractures (type II) were noted. The valve remains implanted. No adverse patient effects have been reported.

Elective explant (n=1, total, n=1 pediatric)
One MDR reported a case of a 15 year old male who had the TPV explanted electively after 11 weeks for a larger mechanical valve implant. Prior to explant the valve was functioning normally. No adverse patient effects were reported.

Erosion (n=1 total, n=0 pediatric)
One erosion event has been reported in the current time period involving a 38-year-old male who presented with increased LV pressure and severe heart failure. Catheterization revealed the valve eroded into ascending aorta with a resultant shunt into the pulmonary artery. The conduit was successfully replaced with no adverse patient effects. *Note that this event type had not been previously reported.*

RVOT obstruction (n=1 total, n=0 pediatric)
One report was received for RVOT obstruction. This was in an adult patient

Heart Block (n=1 total, n=0 pediatric)
One report was received for heart block. This was in an adult patient

POSTMARKET DATA: POST-APPROVAL STUDIES (PAS)

As a condition of approval, the sponsor is required to conduct two post-approval studies.

Summaries of PAS Studies

Study # 1 – Long-term device performance

A prospective, non-randomized, multi-center, historically controlled observational study, designed to follow up subjects from the IDE to 5 years. The hypothesis is that the percentage of subjects with freedom from TPV dysfunction at 5 years is >36% where TPV dysfunction is:

- RVOT reoperation for conduit dysfunction or device-related reason OR
- Catheter re-intervention 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)

Secondary outcome endpoints include

- Percent patients with procedural success
- Percent subjects with serious procedural adverse events
- Percent subjects with serious device-related adverse events
- Stent fracture
- Re-intervention on the TPV

Study # 2 – Device performance in a representative population

This is a prospective, non-randomized, multi-center study of 100 subjects. The hypothesis is that the percentage of subjects with acceptable hemodynamic function at 6 month is $\geq$75%. The primary endpoint is the percentage of subjects with acceptable hemodynamic function at 6 months as defined as:

- Mean RVOT gradient less than or equal to 30 mmHg AND
- Less than moderate severity of pulmonary regurgitation AND
- No RVOT conduit reoperation or catheter re-intervention since implant

Secondary outcome endpoints include

- Percent patients with procedural success
- Percent subjects with serious procedural adverse events
- Percent subjects with serious device-related AE at 6 months post-implant
- Incidence of serious device-related AE during full follow-up period
- Stent fracture
- Re-intervention on the TPV

PAS #1 STUDY RESULTS

Interim Results Presented at 2011 PAC

Of the 169 subjects enrolled in the study, 150 were implanted among five study centers. As of the cutoff date there were 141 of the original 150 subjects remaining in the study.

Safety

In Study # 1 there had been no deaths since the PAS began and 12 subjects (8.0%) with serious device-related AE (including 8 pediatric), for a rate of 5.6 per 100 person-year including:

- Major stent fracture with stenosis (6 – 4 pediatric, 2 adult)
- Major stent fracture without stenosis (1 pediatric)
- Minor stent fracture (1 pediatric)
- Stenosis without stent fracture (2 pediatric)
- Endocarditis (2 adult)

The 12 device-related cases resulted in 8 reinterventions, including 7 TPV replacements and 1 surgical conduit repair. All 7 TPV replacements were associated with major stent fracture (6 were also associated with valve stenosis). The surgical conduit repair was associated with valve stenosis without stent fracture. The reintervention rate was 3.7 per 100 person-years.

Update for the 2012 PAC

As of the cutoff date for this report (May 23, 2012), there were 135 of the original 150 subjects remaining in the study. The mean age was 22.0, with a minimum of 7, median of 19 and maximum of 53. Males accounted for 64% of subjects. Of the 15 subjects no longer remaining in the study

- 4 had died
  - 2 of these 4 occurred prior to the start of the PAS
  - 1 of the remaining 2 was a pediatric subject
- 6 had surgical conduit replacement
  - 4 of these 6 occurred prior to the start of the PAS
  - 1 of the remaining 2 was in a pediatric subject – a 17 year old male with endocarditis
- 4 were lost to follow-up, and
- 1 was withdrawn from the study.

The subject accountability data are stratified by each follow-up time point in the table below.

Subject Accountability			
Follow-up Visit	**Expected # of Subjects**	**Actual # of Subjects**	**Percent Completed**
Discharge	148	148	100.0%
3 month	148	146	98.6%
6 month	146	143	97.9%
1 year	146	141	96.60%
2 year	144	137	95.1%
3 year	105	97	92.4%
4 year	40	31	77.5%
5 year	7	7	100%

Benefit

The mean RVOT gradient found at various follow-up times is depicted below. The mean RVOT gradient has changed very little during the four years of follow-up:

Visit	n	Mean RVOT gradient (mm Hg)
Pre-implant	148	32.1
6 months	142	17.6
1 year	140	18.7
2 years	136	17.6
3 years	92	18.1
4 years	31	17.7
5 years	7	14.9

The degree of TPV regurgitation at various follow-up times is depicted below:

	None	Trace	Mild	Moderate	Severe
Pre-implant	8 (5.3)	5 (3.3)	18 (12.0)	45 (30.0)	71 (47.3)
6 months	106 (76.3)	29 (20.9)	4 (2.9)	0 (0)	0 (0)
1 year	110 (79.1)	20 (14.4)	8 (5.8)	1 (0.7)	0 (0)
2 years	94 (70.7)	30 (22.6)	9 (6.8)	0 (0)	0 (0)
3 years	64 (72.7)	18 (20.5)	6 (6.8)	0 (0)	0 (0)
4 years	23 (76.7)	1 (14.3)	0 (0)	0 (0)	0 (0)

Safety

In Study # 1 there have been two deaths since the PAS began. There have been 16 subjects (10.7%) with serious device-related events so far (including 10 pediatric subjects), for a rate of 4.6 per 100 person-year. The 16 cases included the following:

- Major stent fracture with stenosis (6 – 4 pediatric, 2 adult)
- Major stent fracture without stenosis (1 pediatric, 1 adult)
- Minor stent fracture (1 pediatric)
- Stenosis without stent fracture (2 pediatric, 1 adult)
- Endocarditis (2 adult, 1 pediatric)
- Tricuspid regurgitation (1 adult)

The 16 device-related cases resulted in 12 reinterventions including 8 interventions in pediatric subjects. Overall, the interventions included 8 TPV replacements and 4 surgical conduit repairs. Seven (7) of the 8 TPV replacements were associated with major stent fracture (6 which were also associated with valve stenosis). The other TPV replacement was associated with valve stenosis but no stent fracture. The 4 surgical conduit repairs were associated with valve stenosis with and without stent fracture, mitral regurgitation, and endocarditis. The reintervention rate was 3.5 reinterventions per 100 person-years.

PAS #2 STUDY RESULTS

Interim Results Presented at 2011 PAC

As of June 10, 2011, 63 subjects were catheterized, and 51 were implanted with a Melody TPV. All 51 subjects remained in the study, with a mean follow-up time of 2.4 months. Sixteen subjects were assessed at their 6-month visit. The mean age was 19.6 with a minimum of 5, median of 17 and maximum of 45

Safety

There were no deaths and 8 subjects had serious procedure-related AE (15.4%), including 4 pediatric subjects. These included:

- Perforation of pulmonary artery and embolization of other stents (Pediatric)
- RVOT conduit rupture (2 – 1 pediatric, 1 adult)
- CNS paresthesias (Pediatric)
- Venous thrombosis (Adult)
- Sepsis (Pediatric)
- Hypotension (Adult)
- Ventricular tachycardia (Adult)

These procedure-related events resulted in 3 reinterventions, including 2 TPV replacements (for the two RVOT conduit ruptures) and 1 surgical conduit repair, in the case of the subject with a perforated pulmonary artery, who was subsequently exited from the study.

There were 3 subjects with serious device-related AE in study # 2, for a rate of 29 per 100 person years. These included sepsis, ventricular tachycardia, and one with small bowel obstruction, pneumonia, and endocarditis. All 3 subjects were also classified as having serious procedure-related events. There were no reinterventions in this group.

Update for the 2012 PAC

As of May 23, 2012, there have been 127 subjects consented and enrolled for possible implantation of a Melody TPV in which 11 subjects did not meet the implant indication and were exited. One hundred sixteen (116) subjects were catheterized, 98 subjects had a Melody TPV implant attempted, and 97 were implanted. As of the cutoff date, 93 subjects remain in the study (One subject was never implanted, one withdrew, 2 were explanted, and one had conduit replacement), with a mean follow-up time of 7.7 months. Of 69 subjects due for a 6-month assessment, 68 were assessed at their 6-month visit. The mean age was 20.0 with a minimum of 5, median of 17, and maximum of 50. Males accounted for 66% of subjects.

Benefit

The mean RVOT pre-implant was 33.1 mm Hg. Mean RVOT gradient was 14.0 mm Hg at 6 months (n = 63) and 14.2 mm Hg at one year (n = 41). The amount of TPV regurgitation during follow-up is shown below:

Visit	Degree of TPV regurgitation	n (%)
Pre-implant	None	2 (3.9)
	Trace	2 (3.9)
	Mild	6 (11.5)
	Moderate	20 (38.5)
	Severe	22 (42.3)
6 months	None	44 (68)
	Trace	19 (29)
	Mild	2 (3)
1 year	None	26 (62)
	Trace	10 (24)
	Mild	6 (14)

Safety
There have been no deaths.

Twenty of the 116 catheterized subjects (17.2%) have experienced 28 definite or possible serious procedure-related AEs, including 10 pediatric subjects. These included:

- Perforation of pulmonary artery and embolization of other stents (Pediatric)
- RVOT conduit rupture (6 – 3 pediatric, 3 adult)
- Endocarditis (2 – 1 pediatric, 1 adult)
- Venous thrombosis (2 – 1 pediatric, 1 adult)
- Arrhythmia (2 – one Ventricular tachycardia, one specified, both adult)
- CNS paresthesias (Pediatric)
- Sepsis (Pediatric)
- Respiratory unspecified (Pediatric)
- Minor hemorrhage (Pediatric)
- Thrombosis of TPV (Adult)
- Valve regurgitation (Adult)
- Coronary compression (Adult)

These events resulted in 10 reinterventions, including 5 TPV replacements (for the four RVOT conduit ruptures and one valve regurgitation), and 3 surgical conduit repair (for a perforated pulmonary artery, a compressed coronary artery, and a case of endocarditis), and 2 covered stents (for RVOT conduit ruptures). The reintervention rate was 16.8 per 100 person-years.

There were 10 subjects with serious device-related adverse events in Study # 2 (including 3 pediatric subjects). Nine of the 10 subjects with serious device-related adverse events were also classified as having serious procedure-related adverse events, indicating extensive overlap between the two classifications. The only serious device-related adverse event reported in a subject without a serious procedure-related adverse was a case of atrial flutter.

POSTMARKET DATA: LITERATURE REVIEW

Literature Presented to 2011 PAC

A literature review presented in 2011 included 5 studies which followed implanted subjects prospectively for adverse events. These studies involved 265 attempts at implantation. One (McElhinney) involved a large subset of subjects from the IDE study.

Procedure-related adverse events

There were 21 procedure-related AE (7.9%) in the 5 studies, including:

Event	Number
- Ventricular tachycardia	6
- RVOT rupture	5
- Guidewire injury with pulmonary artery perforation	3
- Rupture of high pressure balloon at post-dilatation	3
- Femoral vein thrombosis	1
- Death from intracranial hemorrhage and coronary artery dissection	1
- Damage to tricuspid valve chordae	1
- Hypercarbia and elevation of left ventricular filling pressure	1

Follow-up

Three studies[1-3] were small (total 33 subjects followed for a mean of 6 months), and reported no adverse events. The other 2 studies involved 124 and 108 subjects and it was estimated that they involved approximate follow-up lengths of 91[4] and 275 person-years[5] respectively.

Author	Estimated person-yrs	Fractureper 100 P-Y	Re-interventions (per 100 P-Y)	Other
McElhinney	91	25 (27)	11 (12)	2*
Nordmeyer	275	24 (1st year) (22)	9 (3)	NA

* Tricuspid regurgitation and pulmonary hypertension with right ventricular hypertrophy

Reinterventions

Of the 20 reinterventions, 14 were replacement TPVs, 5 were explants with surgical conduit repair, and one was dilatation of the TPV. Of the 14 subjects who received TPV replacement, 12 were the result of stent fracture with resultant RVOT obstruction, and the other 2 were the result of RVOT obstruction without stent fracture. Of the 5 explants with surgical conduit repair, three (3) were the result of endocarditis, one (1) was the result of a pseudo-aneurysm, and one (1) was a result of conduit rupture at the initial implantation.

The McElhinney study performed a Kaplan-Meyer analysis of freedom from reintervention, and found a freedom from reintervention rate of 93.5% at one year and 87.6% at two years.

Stent fractures

As noted in the above table, there were 49 stent fractures noted in the two major studies, for an overall rate of 23 per 100 person-year. The McElhinney study found a freedom from stent fracture rate of 77.8% at 14 months.

Deaths

There was one death associated with the initial implant procedure. Other than that, there were no deaths reported in the McElhinney or Zahn study. There were four deaths (1.5 per 100 person-year) reported in the Nordmeyer study. One was the result of sepsis from a chest infection, two were the result of arrhythmias, and one was the result of cardiogenic shock.

Other adverse events

McElhinney reported two, including pulmonary hypertension and tricuspid regurgitation.

Limitations of literature assessment:

Limitations of these studies included lack of information on length of follow-up and how vigorously adverse events were sought for – making it difficult to calculate rate of adverse events or to make valid comparisons between studies.

Review of Literature Since 2011 PAC

A literature search was conducted through PubMed and on July 27, 2012 for articles published after June 2011 to identify additional references since last year's review. The search involved 16 hits. Articles were then excluded from full review on the basis of the following criteria after review of the abstracts:

- Did not involve adverse events in human subjects (3 exclusions)
- Involved only the U.S. clinical trial – already discussed (3 exclusions)
- Did not involve use of the Melody TPV (2 exclusions)
- Involved only use of the Melody valve in the tricuspid position (3 exclusions)
- Case reports (4 exclusions)

After excluding studies that were excluded on the basis of the above criteria, only one study remained[6]. This was a multi-center, observational prospective cohort registry study. The median age of the subjects was 24 with a range of 11-65.

Adverse Events

There were four "early" major adverse events (6.3%) in the study, including the following:

- Ventricular fibrillation
- Pulmonary valve embolization
- Subdural hematoma
- One seriously ill patient died of exacerbation of pre-existing conditions

Other than the one death, the other three events were treated successfully.

Follow-up was for a median of 30 months, with a range of 12 to 48 months. Major adverse events included the following:

- Atrial fibrillation, treated with cardioversion
- Bacterial endocarditis (2) requiring explanation (Both refused antibiotic prophylaxis).
- Stent fractures requiring second Melody valve implantation (2 cases)
- Death due to respiratory failure due to severe scoliosis
- Death due to progression of severe hepatic failure
- Death due to heart failure

Precise follow-up times were not provided for the study, but if one assumes that the mean follow-up was similar to the median follow-up period of 30 months, then we can calculate that the rate of major adverse events after the first month was 8 events divided by 152.25 person-years = 5.3 events per 100 person-years. Of note, it appears that four of the 8 events were obviously related to the device (the two stent fractures and cases of endocarditis), while the other four events don't appear to have a relationship to the device.

Reinterventions

Four (4) reinterventions were reported in the study, noted above (two surgical explantations for bacterial endocarditis and two Melody valve replacements for stent fractures).

Stent fractures

There were 10 stent fractures (8 minor, and 2 major, requiring reinterventions), for an overall rate of 6.6 per 100 person-year.

Assessment of literature:

Given that subjects were clinically evaluated at discharge, one month post-procedure, three months, six months, one year, and annually thereafter, and that fluoroscopy was used to identify stent fractures at six months, one year, and annually thereafter, it would seem that identification of adverse events would have been reasonably complete. However, no information on loss to follow-up was provided. Loss to follow-up could have led to study bias towards low rates, which could have accounted for the relatively low reintervention rate (2.6 per 100 person-years in this study compared to 3.5 per 100 person-years in PAS study # 1 and 16.8 per 100 person-years PAS study # 2), as well as a low rate of total stent fractures compared to earlier literature experience. A comparison of major stent fracture rate in this study with other studies would be problematic because of small numbers (2 cases in this study) and therefore large confidence intervals (total stent fracture rates could not be compared between this study and the PAS studies because the PAS studies did not report minor stent fractures).

Comparison of device- or procedure-related events from this publication to other studies is not possible because this study made no attempt to discern the device- or procedure-relatedness of adverse events.

All four deaths appear to have been due to progression of pre-existing illness.

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