Pediatric Advisory Committee

September 11, 2012

Medtronic Melody® Transcatheter Pulmonary Valve (TPV) & Ensemble® Transcatheter Valve Delivery System H080002

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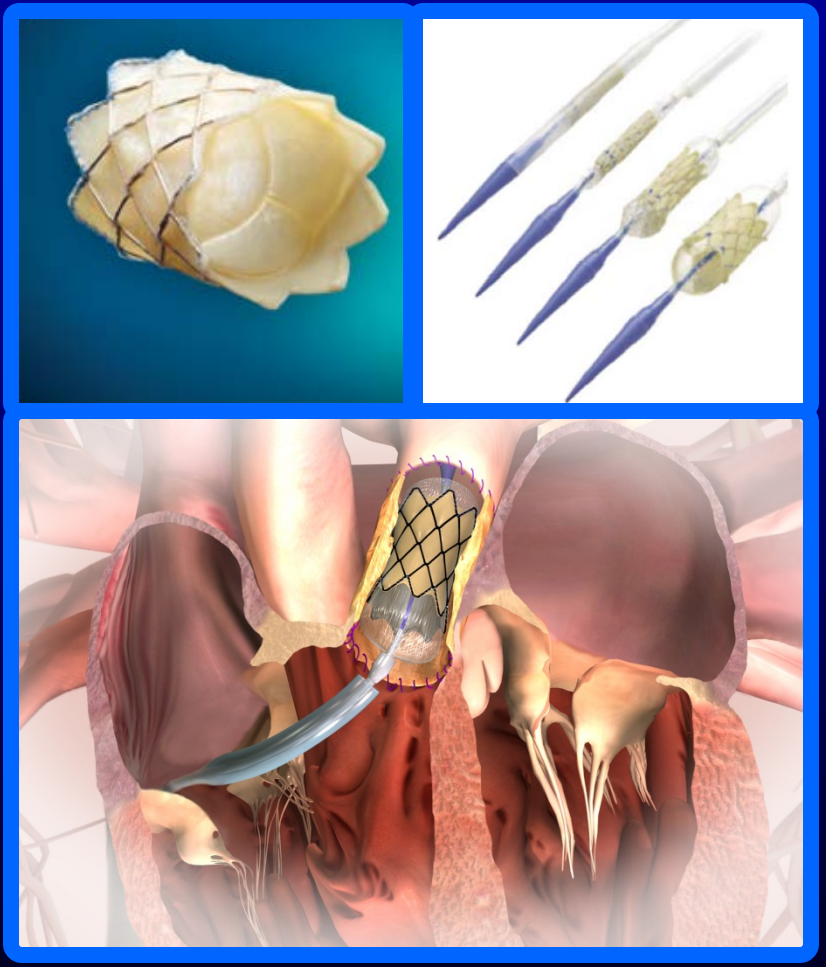
Melody® TPV Device Description

- The Medtronic Melody® Transcatheter Pulmonary Valve (TPV)
  - Adjunct to surgery in pediatric and adult patients with dysfunctional prosthetic Right Ventricular Outflow Tract (RVOT) conduit
  - Bovine jugular vein with native valve sutured into platinum iridium stent
  - Sizes 18mm, 20mm, and 22mm
- The Ensemble® Transcatheter Valve Delivery System
  - Balloon-in-balloon catheter
  - 22 Fr crossing profile



Photos from www.medtronic.com

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.

Options for Dysfunctional RVOT Conduit

- **Prior to Melody TPV**
  - Operative repair
  - Bare metal stents
    - Off-label use
    - Allowed full regurgitation but did extend time between open-heart surgeries
    - Stent fractures of 43% (Peng, et al) [1]
- **Melody TPV**
  - Extend time between open-heart surgeries
  - Address post-procedural pulmonic regurgitation
    - Beating heart procedure

[1] Peng LF et al. *Endovascular stenting of obstructed right ventricle–to–pulmonary artery conduits*: a 15-year experience. Circulation. 2006;113: 2598–2605.

Regulatory History

Melody IDE Study G050186 – 2006

- *Prospective, non-randomized, multi-center clinical study*
- *Enrolled 150 patients*

Humanitarian Use Device (HUD) designation –2007

Humanitarian Device Exemption (HDE)

- *99 IDE patients at data lock (December, 2008)*
- *Professor Bonhoeffer's U.K. study*
- *FDA Circulatory System Devices Panel – July, 2009*
- *HDE Approval – January, 2010*

Post-Approval Studies

- *PAS #1 – long term follow up of 150 IDE patients*
- *PAS #2 – 100 newly enrolled patients (representative population)*

Pediatric Advisory Committee – September 2011

Annual Distribution Number (ADN)

- Melody TPV: ADN* = 2,996 at time of HDE approval
- US distribution of Melody TPV
  - 2010: 524 Melody
    - **~ 59% in pediatric patients**
  - 2011: 719 Melody
    - ~ 72% implanted
      - ages known for 548 of the 561 implantations
        - **~57% in pediatric patients**

* ADN has been redefined by the recent 2012 FDASIA legislation, but this is not relevant to today's discussion.

Pre-Market Patient Demographics

Melody IDE – 99 Patients

- **Mean Age: 20.6 ± 9.2 years [7-44]**
  - 65 pediatric patients (≤ 21 years)
- **Previous open procedure: 2.3 ± 1.0 [1-6]**
  - homograft: 77%
- **Underlying Abnormality**
  - Tetralogy of Fallot (53%)
  - Transposition of Great Vessels (10%)
  - s/p Ross Procedure (17%)
- **Pulmonary Stenosis Indication: 41%**
  - Combined PR/PS: 20%

IDE Primary Probable Benefit Results

At 6 months with Age Stratification

Short-term Effectiveness	**≤ 21 years**	> 21 years
# of Subjects Implanted > 24 hours	**60**	29
# of Subjects Implanted with 6 months follow-up	**45**	19
# of Subjects with Acceptable Hemodynamics at 6 months	**38**	18
Subjects with Acceptable Hemodynamics at 6 months ***(Success: ≥ 75%)***	**84.4%**	94.7%

IDE Primary Safety Results

At 6 months with Age Stratification

Mortality	**≤ 21 yrs**	> 21 yrs
# of Subjects Catheterized	**65**	34
# of Subjects Free of Procedure-Related Death at 6 months	**65**	33
# of Subjects Free of Device-Related Death at 6 months	**65**	34
Subjects Free of Procedure or Device-Related Death ***(Success: ≥ 95%)***	**100%**	97.1%

Morbidity	**≤ 21 yrs**	> 21 yrs
# of Subjects Catheterized	**65**	34
# of Subjects with Serious Procedure-Related AE	**2**	2
# of Subjects with Serious Device-Related AE at 6 months	**1**	0
# of Subjects with Serious Procedure or Device-Related AE at 6 months	**3**	2
Subjects with Serious Procedure or Device-Related AE ***(Success: < 30%)***	**4.6%**	5.9%

IDE Secondary Safety Results

Event	Subjects (n=89)	Rate
Stent fracture	**16**	**18%**
Minor	**11**	**12.4%**
Major	**5**	**5.6%**
Valve stenosis	**6**	**6.7%**
Re-intervention	**6**	**6.7%**
Conduit exchange	1	1.1%
Worsening heart failure	1	1.1%
Embolization	0	
Endocarditis	0	
Thrombosis	0	
Pulmonary thromboembolism	0	
Hemorrhage	0	
Structural deterioration	0	
Non-structural dysfunction	0	
Paravalvular leak	0	

Medical Device Reporting (MDR)

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Medical Device Reporting (MDR) Method

CDRH MAUDE (Manufacturer and User Facility Device Experience) Database

MDR Search Criteria :

- Brand Name: containing “Melody” Valve
- Date Report Received: 7/2/2011 to 7/1/2012 (Data lock date)

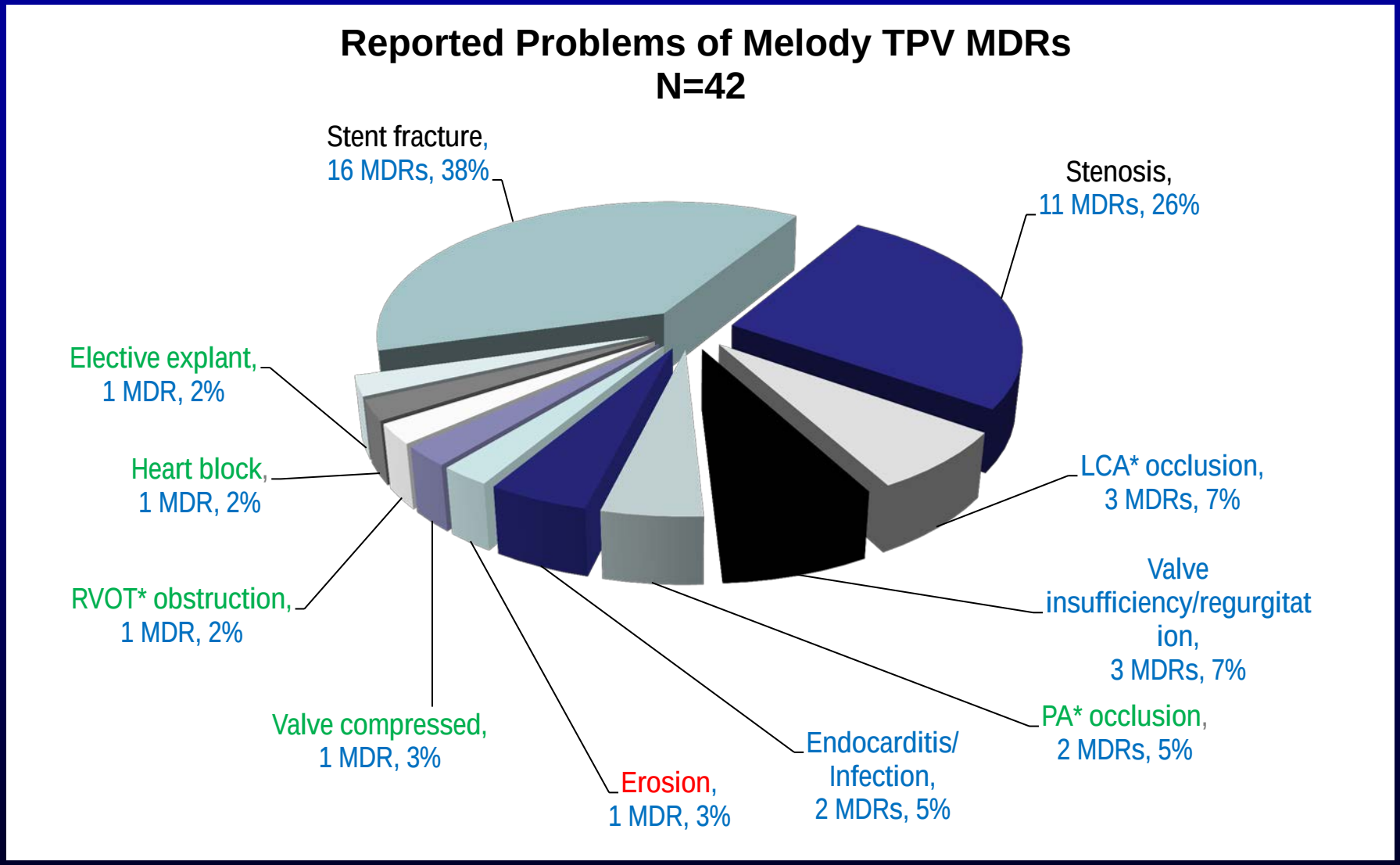
Search Result: 42 MDRs

- The 42 MDRs were exported to Excel Spreadsheets for further review.

Overview of 42 Melody TPV MDRs

- Received by FDA between July 2, 2011 and July 1, 2012
- Country:
  - » US 31
  - » OUS 5
  - » Unknown 6
- Patient Gender:
  - » Male 27
  - » Female 12
  - » Unknown 3
- Patient Age:
  - » Pediatric (< 22) 17 (Range 7-20; Mean 14)
    - Child (2-11) 5
    - Adolescent (12-21) 12
  - » Adult (≥ 22) 14 (Range 24-47; Mean 33)
  - » Unknown 11

Reported Problems



***LCA: Left coronary artery; *PA: Pulmonary artery; *RVOT: Right ventricular outflow track**
***Reported problems marked in Black: Top reported problems; Blue: problems reported in previous year.**
Green: new problems not reported in previous year; Red: new problem not in device labeling;

Event Type of 42 Melody MDRs

	Pediatric n=17	Adult n=14	Age Unknown n=11
Death, n=3	1	2	0
Serious Injury*, n=30	12	9	9
Malfunction**, n=9 (no interventions required)	4	3	2

* Serious Injury per regulatory definition (CFR 803.3) includes an event that is life-threatening or results in permanent impairment or necessitates medical or surgical intervention(s).

** Malfunction event is defined as device not performing as intended, but no patient adverse effects and no intervention(s) required.

Reported Problems of the 3 Deaths

One Pediatric Patient:

Endocarditis

- A 19-y-o male patient had a history of endocarditis.
- High gradients and suspected endocarditis 2 yrs post implant.
- Renal failure, required a RVAD. A balloon dilatation fractured the stent.
- TPV explanted.
- Expired 40 days post TPV explant.
- Suspected cause of death:
  - Multisystem organ failure due to severe septic shock from endocarditis

Two Adult Patients:

PA occlusion

- A 38-y-o male.
- PA occluded post implant, cardiac tamponade, brain injury.
- Support withdrawn, p't expired.

Unknown cause of death

- A 29-y-o male.
- A stent fracture at 3 months post implant.
- Pt expired at 28 months post implant.
- Arrhythmia and viral illness with blood culture (-) ; Cause of death unknown

Event Category

Time to Event Occurred (TTEO) of 42 MDRs

The 42 MDRs/events were categorized based on TTEO

- time between Date of Implant and Date of Event, or
- implant duration specified in the Event Text.

- Peri-procedural events: n=5

  Events occur <u>within</u> 24 hours of TPV implant

- Post -Implant events: n=37

  Events occur <u>after</u> 24 hours of TPV implant

Peri-Procedural* Events, n=5

Reported Problem	Pediatric	Adult	Unknown
Coronary Artery Occlusion, n=3	1	2	0
Pulmonary Artery Occlusion, n=2	1	1	0
Total	2	3	0

* Peri-procedural events: Events occur within 24 hours of TPV implant

Peri-Procedural Event and Intervention(s)

Reported Problem	Interventions Required
Coronary Artery Occlusion (3) (1P)	Stenting (1) Explant (3) ECMO* (1) Heart Transplant (1)
Pulmonary Artery Occlusion (2) (1P)	Explant (1) Surgery (1)

*ECMO: Extracorporeal Membrane Oxygenation

Post-Implant* Event, n=37

Reported Problem	Pediatric	Adult	Age Unknown
Stent fracture, n=16	6	5	5
Stenosis, n=11	3	4	4
Valve insufficiency/ regurgitation, n=3	**2**	0	1
Endocarditis, n=2	**2**	0	0
Erosion, n=1	**0**	1	0
Valve compressed, n=1	**1**	0	0
RVOT obstruction, n=1	**0**	1	0
Heart block, n=1	**0**	0	1
Elective explant, n=1	**1**	0	0
Total	**15**	11	11

* Post -Implant events: Events occur after 24 hours of TPV implant

Post-Implant Event, n=37

Reported Problem	Intervention required
Stent fracture, n=16	Explant (2), 2nd TPV (5), Stenting (2), Valvuloplasty (1), No AE* (9).
Stenosis, n=11	Explant (4), Angioplasty (3), Valvuloplasty (2), 2nd TPV (2),
Valve I/R*, n=3	Explant (2), Valvuloplasty (1)
Endocarditis, n=2	Explant (2), Antibiotics (2), Angioplasty (2), RVAD* (1),
Erosion, n=1	Conduit replaced (1)
Valve compressed, n=1	Angioplasty (1)
RVOT obstruction, n=1	Explant (1)
Heart block, n=1	Pacemaker (1)
Elective explant, n=1	

*One patient might require more than one interventions, therefore the total number of interventions required does not equal to the total number of pediatric patient.
*AE: Adverse Effect *I/R: Insufficiency/Regurgitation *RVAD: Right ventricular assist device

Stent Fracture (n=16)

- Age: 11/16 reports age known, mean age 22 (range 7-47)
  - Pediatric: 6 patients, mean age 13 (range 7-18)
  - Adult: 5 patients, mean age 33 (range 25-47)
- Gender: 15/16 reports gender known
  - Male: Female 11 : 4
- Time to diagnosis: 3 – 49 months post implant
- Event type:
  - 7 patients: required intervention(s) -- 1 death and 6 injury events
  - 9 patients: no interventions required

	Pediatric n=6	Adult n=5	Unknown Age, n=5
Death, n=1	0	1?	0
Injury, n=6	2	1	3
Malfunction (no interventions required), n=9	4	3	2

?: Cause of death was unknown, but the patient presented stent fx at 3 months and arrhythmia and viral illness at 28 months.

- Stent Fx Progression:
  - Noted in 4 of 16 MDRs; Asymptomatic➔ required intervention(s) subsequently

Stent Fracture: Pediatric Patient (n=6)

Pt Age	Pt Gender	TTEO (month)	Reported problem	S & S*, Findings	Interventions Required
Stent fracture, 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
Stent fracture required interventions, n=2					
15	M	7	Stent fx		Stenting & 2nd TPV
16*	M	0	Pre-post 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
		8	Longitudinal stent fxs at a pressure of 6 ATM* occurred post balloon 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	Snaring the ruptured balloon. No other adverse patient effects

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

Summary of MDRs

(N=42 MDRs for the past 1 year)

- 3 deaths with reported problems:
  - endocarditis/infection (pediatric pt)
  - PA occlusion (adult)
  - unknown cause of death (adult)

30 injuries

9 malfunctions

- Top reported problem – Stent fracture
  - consistent with findings of premarket study and first year of post-market MDRs.
  - more than half of the patients with stent fracture did not have adverse effects or require interventions

- One erosion injury event – in an adult

  Erosion not listed in device Instruction for Use (IFU)

- Pediatric – 17 patients, including 1 death, 12 injuries and 4 malfunctions

Melody Post-Approval Study Considerations

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Melody HDE Conditions of Approval

FDA Circulatory System Devices Advisory Panel of July 2009 recommended that a post-approval study (PAS) be conducted

- hypothesis driven
- have comparators
- be powered to look for severe low frequency adverse events

On approval of the Melody HDE application, FDA required 2 PASs

- PAS #1 with the premarket cohort followed for 5 years
- PAS #2 with 100 new subjects followed for 5 years

Post-Approval Study 1: Continued follow-up of premarket cohort

<u>Purpose</u>: to assess long-term safety / effectiveness

- 150 subjects continued from premarket study from 5 sites
- 5-year follow-up with annual clinical assessment
- Primary outcome: TPV dysfunction:
  - RVOT reoperation OR
  - Catheter reintervention on the TPV OR
  - Hemodynamic dysfunction of the TPV
- Safety outcomes
  - Serious procedural- and device-related adverse events
  - Stent fracture
  - Death (All cause, procedure- and device-related)

Post-Approval Study 1: Clinical Assessment Schedule

Procedure	3 mos	6 mos	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Clinical assessment	X	X	X	X	X	X	X
Transthoracic echocardiogram (TTE)	X	X	X	X	X	X	X
Chest X-ray	X		X	X	X	X	X
Echocardiogram (ECG)		X					
Fluoroscopy		X					
Urinalysis		X	X	X	X	X	X
Cardiovascular magnetic resonance imaging (CMR)		X					
Cardiopulmonary exercise testing (CPET)		X	X	X	X	X	X

Post-Approval Study 2:
New Enrollment Study

<u>Purpose</u>: to assess safety and effectiveness in representative population of providers and patients

- 100 new subjects from 10 sites
- 5-year follow-up with annual clinical assessment
- Acceptable hemodynamic function
- Safety outcomes
  - Serious procedural- and device-related adverse events
  - Stent fracture
  - Death (All cause, procedure- and device-related)

Definitions of Adverse Events for the PAS Studies

- **Serious adverse event: Results in:**
  - Death
  - Life threatening situation
  - Requires intervention to prevent permanent impairment of body structure or function
  - Requires hospitalization or prolongation of existing hospitalization

- **Device-related:** The event was associated with the device by chronology and physiology and was caused by the device.

- **Procedure-related:** The event was associated with the implant procedure by chronology or physiology and was caused by the implant procedure.

Subject Accountability

- **Pre-market IDE study**
  - Approved for total of 150 subjects
    - HDE application submitted August 29, 2008
      - 30 subjects with 6 months follow-up
      - An additional 69 subjects had been enrolled
    - Primary analysis cohort of 99 subjects supported the HDE application
    - IDE study continued enrolling to 150 subjects
- **PAS #1**
  - 135/150 subjects from premarket cohort remain in the PAS study (83 pediatric, 52 adults)
    - 6 surgical conduit replacements, 4 deaths, 4 lost to f/u, 1 withdrawal
    - Followed for 30 months in PAS
- **PAS #2**
  - 100 subjects - 98% of enrollment completed
    - 93 of 98 subjects with attempted implant remain in follow-up (60 pediatric, 33 adults)
    - Mean follow-up of 7.7 months

Rates of Serious Device- and Procedure-Related AEs in Melody TPV PAS Studies

Procedure-related

- Study 2:
  20 subjects (10 pediatric) / 116 catheterized = 17%

Device-related

- Study 1:
  16 subjects (10 pediatric) / 350 person-years
  = 4.6 per 100 person-years (Adults)
  = 4.7 per 100 person-years (Pediatric)

- Study 2:
  10 subjects (9 had concurrent procedure-related events, 3 were pediatric)

Procedure-Related Serious AE Study 2

Pediatric	Adults
20 Subjects with Procedure-Related AE	
Perforation of pulmonary artery and embolization of other stents (1). Exited study	RVOT conduit rupture (3)
RVOT conduit rupture (3)	Venous thrombosis (1)
CNS parenthesis (1)	Arrhythmia (2)
Venous thrombosis (1)	Endocarditis (1)
Sepsis (1)	Coronary compression (1)
Endocarditis (1)	Thrombosis of TPV with pulmonary embolis (1)
Minor hemorrhage (1)	Valve regurgitation (1)
Respiratory unspecified (1)	
Of the 20 subjects, 3 required reinterventions	
Surgical conduit repairs (1)	Explant (1)
	Covered stent (1)

Device-Related Serious AEs – PAS # 1

Pediatric	Adults
16 subjects with device-related Serious AE	
Major stent fracture with stenosis (4)	Major stent fracture with stenosis (2)
Major stent fracture without stenosis (1)	Major stent fracture without stenosis (1)
Minor stent fracture (1)	Stenosis without stent fracture (1)
Stenosis without stent fracture (2)	Endocarditis (1)
Endocarditis (2, including 1 death)	Tricuspid regurgitation (1)
Of the 16 SAEs, 12 required reinterventions	
TPV replacements (6)	TPV replacements (3)
Surgical conduit repairs (2)	Surgical conduit repairs (1)

Stent Fractures

- Stent fx as serious device-related event: 8
- Other stent fx (classified as minor): 16
- Total stent fractures: 24; 5.8 / 100 P-Y
- Only 3 (all minor) stent fractures in PAS #2
- Distribution by pediatric vs. adult
  - Major: 5 pediatric, 3 adult
  - Minor: 9 pediatric, 7 adult

Mean RVOT Gradient (mmHg)

- **Study # 1**
  - **-- Pre- implant (n=147)** **Mean = 32.1**
  - – Discharge (n=147) Mean = 17.7
  - – 3 months (n=145) Mean = 17.5
  - – 6 months (n=142) Mean = 17.2
  - – 1 year (n=140) Mean = 18.7
  - – 2 year (n=136) Mean = 17.6
  - – 3 year (n=92) Mean = 18.1
  - – 4 year (n=31) Mean = 17.5
  - -- 5 year (n=7) Mean = 14.9
- **Study # 2**
  - – **Pre-implant** **Mean = 33.9**
  - – Discharge (n=88) Mean = 16.9
  - – 6 months (n=63) Mean = 14.0
  - -- 1 year (n=41) Mean = 14.2

Summary of Literature Review Conducted for 2011 Panel Meeting

- 5 studies with 265 attempted implants
- Procedure-related AE = 7.9%
- Reintervention rate = 5.2 per 100 person-year
- Stent fracture rate = 23 per 100 person-year

Literature Safety Review Methods

- Search of PubMed, July 24, 2012
- Search criteria: Melody, pulmonary, valve
- Articles reporting AEs
- Search criteria identified 16 publications
- 15 were excluded
  - Did not involve AEs in human subjects
  - Involved only the U.S. Clinical Trial
  - Did not involve the Melody TPV
  - Involved use only at tricuspid position
  - Case reports

Literature Safety Review Overview

- 1 study, 63 subjects (All OUS)
  - Butera, et al: Melody TPV Implantation: Results from the Registry of the Italian Society of Pediatric Cardiology
  - Multi-center, observational prospective cohort registry study
  - Age range 11-65

Literature Safety Review
Major Adverse Events

- 63 subjects, entered registry between October 2007 and October 2010
- Followed median of 30 months
- Early major adverse events
  - Ventricular fibrillation
  - Pulmonary valve embolization
  - Subdural hematoma
  - 1 death due to pre-existing conditions
- Late major adverse events
  - Atrial fibrillation
  - Bacterial endocarditis (2)
  - Stent fractures (2)
  - Deaths (3)

Literature Safety Review Reinterventions

- **4 subjects with reinterventions**
  - Surgical explantation (2)
  - Replacement TPV (2)

Literature Safety Review
Stent Fractures

- 10 stent fractures (2 major, 8 minor)
- Rate = 6.6 per 100 person-years
- Similar to rate in PAS studies (5.8 /100 P-Y) but lower than that reported previously in the literature (23 per 100 person years)
- No obvious explanation for the differences

Discussion of Literature Review

- No information on device- or procedure-relatedness
- No information on loss to follow-up
- No restrictions on subjects due to severe pre-existing conditions
- Therefore it is impossible to compare results of this study to postmarket data

Summary from Postmarket Studies

- Reinterventions have occurred in 4.1% of subjects in PAS # 2, which is not statistically different than in the premarket study

- Of 4 reinterventions:
  - 1 surgical conduit repair
  - 1 covered stents
  - 2 explants

- There are no significant findings that differ substantially from last year's presentation. Given the substantial declines in RVOT gradient and the preclusion of the need of additional major surgery, the benefits from this device appear to be substantial compared to its risks

FDA Conclusions and Panel Question

- FDA has not identified any significant new safety trends from the available data.
- FDA concludes that the HDE device remains appropriately approved and labeled for pediatric use.

- FDA will continue routine surveillance including
  - MDR Review
  - Mandated Post-Approval Studies Review
  - Literature Review
- FDA will present Melody data to the PAC in 2013 should any new safety signals arise.

QUESTION: Does the Committee agree with FDA's conclusions and proposed approach.