SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Portable *Ex Vivo* Organ Perfusion System for Donor Hearts
Device Trade Name:	Organ Care System (OCS™) Heart System
Device Procode:	QIK
Applicant Name and Address:	TransMedics, Inc. 200 Minuteman Road, Suite 302 Andover, MA 01810
Date of Panel Recommendation:	April 6, 2021
Premarket Approval Application (PMA) Number:	P180051
Date of FDA Notice of Approval:	September 3, 2021

II. INDICATIONS FOR USE

The TransMedics Organ Care System (OCS) Heart System is indicated for the preservation of donor-after-brain-death (DBD) hearts deemed unsuitable for procurement and transplantation at initial evaluation due to limitations of prolonged cold static cardioplegic preservation (e.g., > 4 hours of cross-clamp time).

III. CONTRAINDICATIONS

The TransMedics OCS Heart System is contraindicated for donor hearts with moderate to severe aortic valve incompetence, observed myocardial contusion, or known unrepaired interatrial or interventricular defects including patent foramen ovale.

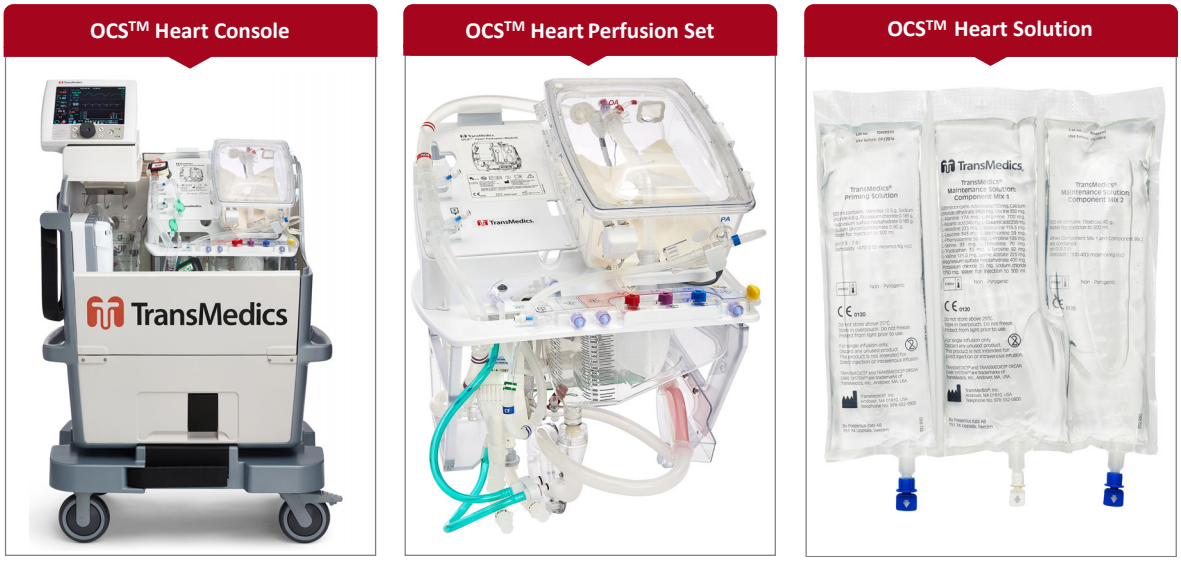
IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the TransMedics OCS Heart System labeling.

V. DEVICE DESCRIPTION

The OCS Heart System, as shown in Figure 1, consists of the OCS Heart Console (Heart Console), the OCS Heart Perfusion Set (HPS), and the OCS Heart Solution Set:

Figure 1: Components of the OCS Heart System



- **Heart Console:**

The Heart Console is the reusable, non-sterile portable base unit for the OCS Heart System that includes the electronics, software, fluid pumping systems, monitoring systems, power supply, batteries, gas cylinder, mobile base, and Wireless Monitor. The Wireless Monitor displays perfusion and pressure parameters and allows the user to evaluate parameters and adjust specific system settings during transport of the donor heart. The Heart Console provides a rigid compartment to house and protect the HPM during transport.

- **HPS:**

The HPS consists of the Heart Perfusion Module (HPM), which is housed within and protected by the Heart Console during transport, and the disposable HPS accessories. The HPM provides a closed circulatory system to protect, maintain, and support the donor heart. It uses a physical conduit to connect to the heart, incorporates various sensors, and interfaces with the Heart Console to oxygenate, warm, and circulate the perfusate. The disposable HPS accessories are intended to:

  - Collect and filter the donor blood.
  - Prime and then infuse the OCS Heart Solution Set into the HPM.
  - Connect the heart to the HPM perfusion circuit.
  - Facilitate access through the aorta for examination of the heart.
  - Infuse cardioplegia to terminate the preservation.

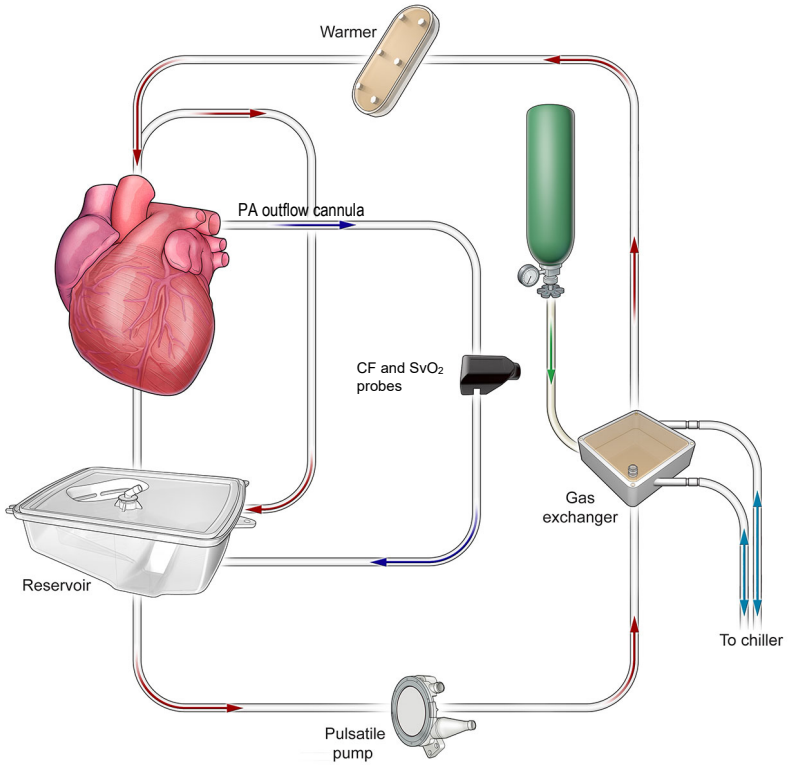
- **OCS Heart Solution Set:**

The OCS Heart Solution Set consists of two proprietary heart preservation solutions: the OCS Priming Solution and the OCS Maintenance Solution. Additives are required at the

time of use that are supplied and added by the user. The OCS Heart Solution Set is not intended to be administered directly to the donor or the recipient.

The OCS Heart System preserves the heart in a near-physiological, beating state by perfusing the heart with a warmed, donor-blood based solution that is supplemented with nutrients and oxygen in a controlled and protected environment, referred to as the circuit, as illustrated in Figure 2. The OCS Maintenance Solution is infused into this circuit. The heart consumes oxygen and nutrients as the blood travels from the aorta through the coronary arteries and returns to the circuit through its pulmonary artery. The OCS maintains the blood at a constant temperature, oxygenates the perfusate, and provides perfusate in a pulsatile flow.

Figure 2: Schematic of the OCS Heart System Circuit



The OCS Heart System controls and monitors the preservation environment. The user can adjust the blood flow rate, solution delivery rate, gas flow rate, and blood temperature within specified ranges to achieve adequate perfusion of the donor heart. The OCS Heart System also calculates and displays pertinent organ perfusion parameters, and provides alarms for parameters out of expected ranges, alarms for low gas and battery capacity, and alarms for sensor failures.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are currently no other alternatives for preservation of donor hearts deemed unsuitable for procurement and transplantation at initial evaluation due to limitations of prolonged cold

static cardioplegic preservation. For patients on the donor heart waitlist, the alternative to receiving a donor heart preserved with the OCS Heart System is waiting for a donor heart preserved with cold static preservation. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The OCS Heart System is commercially available in the following countries: all countries in the European Union, United Kingdom, Australia, Saudi Arabia, United Arab Emirates, Israel, Taiwan, Kazakhstan, Hong Kong and Canada. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with receiving a donor heart preserved using the OCS Heart System, which are typical of the heart transplant procedure:

- Death
- Acute rejection
- Airway anastomotic complications
- Arrhythmia
- Aspiration
- Bleeding (major)
- Emphysema
- Fever
- Focal or systemic major infection
- Gastro esophageal reflux disease
- Graft failure
- Hemodynamic instability
- Hemothorax
- Hepatic dysfunction
- Hyperammonaemia
- Malignancy (post-transplant lymphoproliferative disorder (PTLD)
- Multiple organ failure
- Myocardial infarction
- Neurological dysfunction
- Pancreatitis, peptic ulceration
- Pleural bleeding
- Pleural effusion
- Pneumothorax
- Primary Graft Dysfunction (PGD)
- Pulmonary embolism (PE)
- Pulmonary infarction
- Renal dysfunction
- Respiratory failure
- Sepsis
- Tracheobronchitis/pneumonitis/pneumonia
- Venous thromboembolism (deep venous thrombosis [DVT])
- Wound dehiscence.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

1. Biocompatibility

The applicant performed biocompatibility testing of the HPS in accordance with ISO 10993-1, Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing and USP <661>, Plastic Packaging Systems and their Materials of Construction, as summarized in Table 1.

Table 1: Summary of Biocompatibility Testing

Test	Purpose	Results
Cytotoxicity (minimal essential media elution)	To determine if test article extracts cause cytotoxic effects and cell lysis	Non-cytotoxic
Pyrogenicity (USP <151> rabbit pyrogen)	To determine if the test article extracts causes a febrile response (temperature rise) in intravenously injected rabbits	Non-pyrogenic
Hemolysis (direct and indirect contact)	To determine the potential hemolytic activity on blood in response to the test article and its extract	Non-hemolytic
Sensitization (Guinea pig maximization)	To evaluate the potential of a material or product to cause a sensitizing effect or allergenic reaction over an extended period of exposure	No delayed dermal contact sensitization
Intracutaneous reactivity	To determine if the test article extracts would cause local irritation in the dermal tissues of the test animals	No irritation
Acute systemic toxicity	To determine if the test article extracts would cause acute systemic toxicity	No systemic toxicity observed
Genotoxicity (*in vitro* bacterial reverse mutation; *in vitro* mouse lymphoma assay; *in vivo* mouse peripheral blood micronucleus assay	To determine the potential genotoxicity of a test sample extracts	Non-genotoxic
USP physicochemical Tests (non-volatile residue; residue on ignition; heavy metals; buffering capacity)	To evaluate the safety of products composed of and/or packaged in plastic containers	Met USP limits; no significant extractables

2. Engineering Bench Testing

The applicant performed engineering bench testing on the OCS Heart System to demonstrate that the device meets its product requirements and specifications. The engineering bench testing results are summarized in Table 2.

Table 2: Summary of Engineering Bench Testing

Test	Purpose	Results
OCS Heart System with Solution Delivery Subsystem (SDS)		
Shock and vibration testing	To verify the mechanical integrity and operation of the OCS Heart System with the SDS during transport	Passed
Operational temperature and humidity testing	To verify that the OCS Heart System with the SDS performs to specification when subjected to extreme temperature and humidity	Passed
Operational altitude testing	To verify the function of the OCS Heart System with the SDS during air transport	Passed
Medical device safety	To verify that the OCS Heart System meets the requirements for medical device safety, including electrical safety, per IEC/ANSI/AAMI 60601-1: 2005 +A1:2012	Passed
Electromagnetic compatibility (EMC)	To verify that the OCS Heart System meets the requirements for radio frequency emissions and radio frequency susceptibility per IEC 60601-1-2 4th edition (Group 1, Class A, non-life supporting equipment), CISPR 25, and RTCA DO-160G.	Passed
Heart Console		
Operational rain exposure test	To verify that Heart Console suffers no loss of function or experiences a safety hazard when exposed to rain	Passed
ECG synchronization mode verification	To verify the ability of the Heart Console to deliver coronary perfusion at a regular pattern and velocity during the diastolic phase of the cardiac cycle	Passed
Mechanical design verification	To verify that the Heart Console meets the mechanical specifications and risk mitigation requirements	Passed
Printed circuit board assembly (PCBA) electrical test	To verify that the Heart Console and HPS electrical systems are free from functional defects	Passed
OCS battery pack life cycle test	To verify the use life and shelf life of the OCS battery packs	Passed
Wireless Monitor battery life cycle test	To verify the use life and shelf life of the Wireless Monitor battery pack	Passed

High-speed mixed venous oxygen saturation (SvO2)/ hematocrit (HCT) probe accuracy test	To verify the accuracy of the SvO2/HCT probe	Passed
Zoll X-series defibrillator verification	To verify the adequacy of the Zoll X-series defibrillator for use with the OCS Heart System	Passed
Bluetooth serial port adapter verification	To verify the Bluetooth module meets the product requirements for wireless communication and range	Passed
Gas Cylinder Regulator reliability verification	To verify that the Gas Cylinder Regulator meets the safety and reliability requirements	Passed
Gas Cylinder Regulator performance verification	To verify that the Gas Cylinder Regulator meets the gas flow rate and accuracy requirements	Passed
Transonic flowmeter printed circuit board (PCB) verification	To verify that the flowmeter PCB meets the flow rate range and accuracy requirements	Passed
Gas Cylinder retention strap verification	To verify that the Gas Cylinder retention strap can securely hold a Gas Cylinder over the cylinder diameter tolerance range	Passed
HPS		
Front End Board verification	To verify that the PCBA of the HPM, the Front End Board, meets product performance and RoHS requirements	Passed
Heater Plate and Blood Temperature Sensor accuracy	To verify the accuracy of the components of the Blood Warmer subassembly that are used to measure and control perfusate temperature	Passed
Reservoir blood defoaming test	To verify the ability of the perfusate reservoir of the HPM to separate air from pumped blood	Passed
Reservoir filtration testing	To verify the filtration efficiency of the perfusate reservoir filter to filter particulates 20 microns and larger from blood	Passed
Aorta Connector Cable Tie Tool Force to Cut range	To determine the ideal Force to Cut range for the Cable Tie Tool	N/A; for characterization purpose
Aorta Connector Leak Testing	To verify the robustness of the connection of the heart aorta to the HPS Aorta Cannula when using a combination of Cable Tie Tool and Cable Tie	Passed
Pressure transducer accuracy verification	To verify the accuracy of the pressure transducer used on the HPM	Passed

Maquet oxygenator performance testing	To verify that the oxygenator of the HPM meets product specifications for oxygen transfer and carbon dioxide removal	Passed
Stress test of Maquet oxygenator with reinforced connectors	To verify that the Maquet oxygenator, with its inlet and outlet blood connectors reinforced by TransMedics to prevent disengagement, maintains viability after sterilization, temperature cycling, and pressure challenge	Passed
Tensile testing of HPM tubing connections	To verify the mechanical integrity of the HPM tubing and tubing connections when subjected to tensile loading	Passed
SDS Cassette life testing	To verify that the SDS disposable cassettes can withstand operational use for a minimum of 12 hours	Passed

3. Software Verification and Validation

The applicant performed software verification and validation testing to demonstrate that the OCS Heart System performs as intended. The testing included code review, unit tests, static analysis, system level tests, and validation testing. The device passed all testing and met its requirements. Software documentation was provided in accordance with the FDA guidance document, entitled "Guidance for the Contents of Premarket Submissions for Software Contained in Medical Devices."

4. Cybersecurity

The OCS Heart System incorporates a Wireless Monitor dedicated to the Heart Console. The Wireless Monitor communicates with the OCS Console using one of two redundant communication interfaces - hard-wired or Bluetooth. To address potential cybersecurity risks, the applicant provided information according to the FDA guidance document entitled, "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices," including a cybersecurity threat model and assessment, validation/verification testing (which included penetration testing), and a plan for identifying and responding to emerging cybersecurity issues. Collectively, this information demonstrated that the applicant has appropriate controls in place to identify, protect, detect, respond, and recover from cybersecurity threats per the FDA guidance document.

5. Wireless Technology

The wireless connection between the OCS Console and Wireless Monitor is a peer-to-peer Bluetooth connection. The applicant followed the recommendations presented in the FDA guidance document entitled, "Radio Frequency Wireless Technology in Medical Devices," in the design, testing, and use of the Wireless Monitor.

6. Sterilization

The HPS is sterilized using Ethylene Oxide (EtO). EtO sterilization validation was performed per ISO 11135-1:2007 and demonstrated a minimum sterility assurance level (SAL) of 10^{-6}. The lethality of the EtO sterilization process was demonstrated utilizing the overkill concept of sterilization. EtO and ethylene chlorohydrin (ECH) residuals were evaluated and determined to be below the maximum allowable limits per ISO 10993-7: 2008.

The OCS Heart Solution Set is steam sterilized. The sterilization cycle was validated to achieve a minimum SAL of 10^{-6} according to U.S. Pharmacopeia USP28-NF23 and European Pharmacopoeia 5th ed.

7. Shelf Life Testing

Package integrity and shelf life testing was completed for the HPS and OCS Heart Solution Set in accordance with ASTM F1929-98, ASTM F88:2000, ANSI/AAMI/ISO 11607-1:2006, ANSI/AAMI/ISO 11607-2:2006, ICH Q1A(R2):2003, ICH Q1B:1996, and USP 35-NF30:2012, where applicable. Shelf life has been established at 42 months for the HPS and 24 months for the OCS Heart Solution Set.

B. Animal Study

In addition to multiple animal studies performed throughout the research and development process, the applicant performed an animal study on the final finished OCS Heart System to evaluate its function of donor heart preservation. A summary of the functional animal study is provided in Table 3.

Table 3: Summary of Animal Study

Animal model	Yorkshire pig
Sample size	2
Test article	OCS Heart System
Methods	Two porcine hearts were instrumented on the OCS Heart System following the clinical instructions for use. The instrumented hearts were each maintained on the OCS Heart System for at least 6 hours. The porcine hearts were beating and perfused during the entire test period; hearts were maintained in ECG Synchronization Mode for a minimum of 30 minutes. The study included at least 30 minutes of car transportation while the heart was preserved and maintained on the OCS Heart System.
Results	The hearts were adequately maintained and perfused on the OCS Heart System according to the predefined protocol and perfusion parameters. The metabolic profile met the acceptance criteria of a stable trend throughout perfusion and a trend of neutral or absorbing venous-arterial differential.
Conclusion	The study results demonstrated that the configuration of the OCS Heart System worked successfully during simulated surgical

	procedures and the OCS Heart System met the performance specifications.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the OCS Heart System for preserving DBD hearts deemed unsuitable for procurement and transplantation at initial evaluation due to limitations of prolonged cold static cardioplegic preservation (e.g., > 4 hours of cross-clamp time) under IDE G140111 (entitled the "EXPAND Heart" study). The data from this study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The EXPAND Heart study was a prospective, single-arm, multicenter study. Patients were enrolled between September 16, 2015 and March 25, 2018 at 9 investigational sites in the U.S. The database for this PMA reflected data collected through June 3, 2019.

The EXPAND Heart study used an independent Data Safety Monitoring Board (DSMB) that was instructed to notify the applicant of any safety or compliance issues and a Clinical Events Committee (CEC) that was responsible for adjudicating endpoint-related events reported during the study. An independent pathology core laboratory was used for evaluation of donor hearts that were preserved using the OCS Heart System but later turned down for transplant.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the EXPAND Heart study was limited to donor hearts and transplant recipient patients that met the following:

   Donor heart prior to preservation:

   - Expected total cross-clamp time of ≥ 4 hours; or
   - Expected total cross-clamp time of ≥ 2 hours PLUS one or more of the following risk factors:
     - Donor age 45-55 years old with no coronary catheterization data; or
     - Donor age ≥ 55 years old; or
     - Left ventricular septal or posterior wall thickness of >12 mm and ≤ 16 mm; or
     - Reported down time of ≥ 20 min, with stable hemodynamics at time of final assessment; or
     - Left heart ejection fraction (EF) of ≥ 40% and ≤ 50%; or
     - Donor angiogram with luminal irregularities with no significant coronary artery disease (CAD); or
     - History of carbon monoxide poisoning with good cardiac function at time of donor assessment; or

- Social history of alcoholism with good cardiac function at time of donor assessment; or
- History of diabetes combined with negative coronary angiogram for CAD.

Donor heart post preservation:

- Final total arterial circulating perfusate lactate level < 5 mmol/L with stable lactate trend.
- Stable coronary flow (CF), aortic pressure (AOP) trends within ranges below after stabilization (certain expanded criteria organs, e.g., left ventricular hypertrophy hearts, may require higher CF and/or AOP to achieve adequate perfusion):
  - Mean AOP: 40-100 mmHg;
  - CF: 400-900 ml/min.

Recipient - day of transplant:

- Registered primary heart transplant candidate.
- Age ≥ 18 years old.
- Signed written informed consent document and authorization to use and disclose protected health information.

Donor hearts and transplant recipient patients were not permitted to enroll in the study if they met any of the following exclusion criteria:

Donor heart prior to preservation:

- Angiogram proven CAD with > 50% stenosis; or
- Cardiogenic shock or myocardial infarction; or
- Sustained terminal EF of < 40%; or
- Significant valve disease except for competent bicuspid aortic valve.

Recipient - day of transplant:

- Prior solid organ or bone marrow transplant; or
- Chronic use of hemodialysis or diagnosis of chronic renal insufficiency; or
- Multi-organ transplant.

2. Follow-up Schedule

Follow-up time points included day of transplant, 24 hours, 48 hours, 72 hours, 7 days, discharge, 30 days, 6 months, and 1 year post transplant, and annually thereafter to 5 years post procedure. Pre- and post-implant assessments included medical and cardiac history, mechanical circulatory or respiratory support, heart graft-related adverse events and serious adverse events, and patient/graft survival. All other adverse events and complications were recorded at all visits.

3. Clinical Endpoints

The primary endpoint was a composite of patient survival at 30 days post-transplant and freedom from severe primary graft dysfunction (PGD), as defined by the International Society for Heart and Lung Transplantation (ISHLT), at 24 hours post-transplant. A performance goal of 65% was pre-specified for the primary endpoint. The hypothesis for the primary endpoint was as follows:

$$H_0: \pi \leq 65\%$$
$$H_A: \pi > 65\%$$

where π represented the composite event rate. If the lower 95% confidence limit for the composite event was less than 65%, the performance goal would be met. The hypothesis was tested at a one-sided significance level of 0.05.

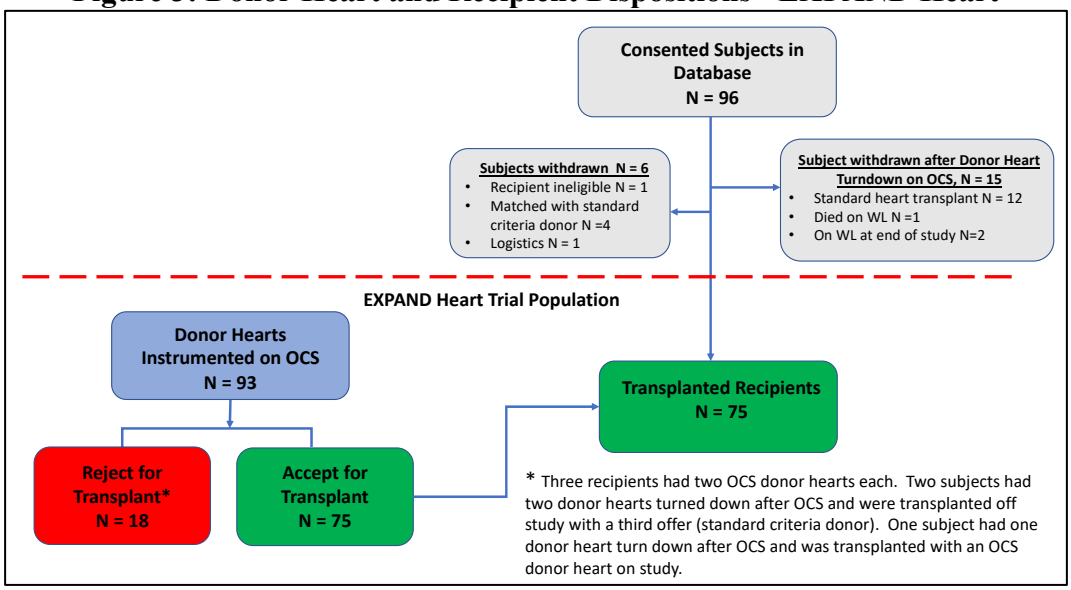
The secondary endpoints included the following:

- Patient survival at 30 days post-transplant.
- Incidence of severe ISHLT PGD (left or right ventricle) in the first 24 hours post-transplant.
- Rate of donor heart utilization (i.e., the percentage of donor hearts successfully transplanted after preservation and assessment on the OCS Heart System).
- Incidence of heart graft-related serious adverse events (HGRSAEs) in the first 30 days post heart transplantation, defined as:
  - Moderate or severe PGD (left or right ventricle; not including rejection or cardiac tamponade).
  - Primary graft failure requiring re-transplantation.

B. Accountability of PMA Cohort

At the time of database lock, a total of 93 donor hearts were preserved using the OCS Heart System and 96 recipient patients enrolled in the study. Ninety (90) patients were matched with a donor heart that was instrumented on the OCS Heart System. Sixteen (16) patients experienced a total of 18 donor heart turndowns following OCS Heart preservation, one of whom was subsequently transplanted with a second donor heart preserved on the OCS Heart System. In all, 75 patients received a donor heart preserved using the OCS Heart System. Twelve (12) of the male recipients received a donor heart from a female donor. The donor heart and recipient dispositions are summarized in Figure 3. The analyses of all study endpoints were based on the transplanted recipient population (N=75).

Figure 3: Donor Heart and Recipient Dispositions - EXPAND Heart



C. Study Population Demographics and Baseline Parameters

The inclusion criteria met by the transplanted donor hearts are summarized in Table 4. Many donor hearts exhibited multiple inclusion criteria. The demographics and baseline characteristics of the recipient patients are summarized in Table 5, which are typical for a heart transplant study performed in the U.S. The majority of recipients were listed as United Network for Organ Sharing (UNOS) status 1A (69.3%) and were on mechanical circulatory support at the time of transplant (64.0%).

Table 4: Inclusion Criteria Met by Transplanted Donor Hearts - EXPAND Heart

Inclusion Criteria Met	Summary Statistics* (N=75)
Expected cross-clamp time ≥ 4hr	28 (37.3%)
Donor age ≥ 55	10 (13.3%)
Left ventricular hypertrophy	17 (22.7%)
Downtime ≥ 20 min	23 (30.7%)
LVEF 40% -50%	21 (28.0%)
Luminal irregularities	7 (9.3%)
Alcoholism	9 (12.0%)
Carbon monoxide as cause of death	1 (1.3%)
Diabetes	2 (2.7%)
Donor age 45-55 with no coronary catheterization data	1 (1.3%)
Donor hearts met single criterion	40 (53.3%)
Donor hearts met multiple criteria	35 (46.7%)

*Categorical measures – no. (%)

Table 5: Recipient Demographics and Baseline Characteristics - EXPAND Heart

Demographics and Baseline Characteristics	Summary Statistics* (N=75)
Age (years)	55.5 ± 12.6
Age > 65	18 (24.0%)
Gender – male	61 (81.3 %)
BMI (kg/m^2)	27.7 ± 4.7
Race	
Asian	2 (2.7%)
Black or African American	12 (16.0%)
White	58 (77.3%)
Other	2 (2.7%)
Not provided	1 (1.3%)
History of mechanical circulatory support	48 (64.0%)
Left ventricular assist device (LVAD)	47 (62.7%)
Right ventricular assist device (RVAD)	0 (0%)
Bi-ventricular assist device (BiVAD)	1 (1.3%)
Extracorporeal membrane oxygenation (ECMO)	0 (0%)
UNOS status	
Status IA	52 (69.3%)
Status IB	22 (29.3%)
Status II	1 (1.3%)
Primary etiology of heart failure diagnosis	
Ischemic cardiomyopathy	26 (34.7%)
Congenital heart disease	2 (2.7%)
Restrictive cardiomyopathy	7 (9.3%)
Non-ischemic cardiomyopathy	24 (32.0%)
Dilated cardiomyopathy	9 (12.0%)
Other	7 (9.3%)
Renal dysfunction	11 (14.7%)
Percent panel reactive antibody (PRA) - mean (range)	7.9% (0-81%)

*Continuous measures - Mean ± SD; categorical measures – no. (%)

D. Safety and Effectiveness Results

1. Primary Endpoint

The analysis of the primary endpoint is summarized in Table 6. Among the 75 recipients of a donor heart preserved on the OCS Heart System, 66 were alive at 30 days post-transplant without severe PGD (left or right ventricle) in the first 24 hours post-transplant. Thus, the

primary endpoint event rate was 88.0%, with a 95% confidence interval of (78.4%, 94.4%). Since the lower bound (78.4%) of the 95% confidence interval is greater than the pre-specified performance goal of 65% ($p < 0.0001$), the null hypothesis is rejected, and the primary endpoint is met.

Table 6: Primary Endpoint Result - EXPAND Heart

Patient survival at 30 days post-transplant and absence of severe PGD (left or right ventricle) in the first 24 hours post-transplant (N=75)	
Proportion - % (no./total no.)[*]	88.0% (66/75)
95% CI for proportion[†]	(78.4%, 94.4%)
Performance goal	65%
p-value[‡]	<0.0001

[*]Simple proportion.
[†]Clopper-Pearson exact confidence interval for a binomial proportion.
[‡]One-sided exact binomial test.

2. Secondary Endpoints

Patient survival at 30 days post-transplant:

The result of patient survival at 30 days post-transplant is summarized in Table 7. One of the 75 recipients of a donor heart preserved on the OCS Heart System experienced a graft failure and underwent re-transplantation using cold static cardioplegic preservation on post-operative day (POD) 6. This patient was terminated from the study. Seventy (70) of the remaining 74 recipients were alive at 30 days post-implant, which led to a patient survival rate of 94.6% at 30 days post-transplant.

Table 7: Patient Survival at 30 Days Post-transplant - EXPAND Heart

Patient survival at 30 days post-transplant (N=75)	
Proportion - % (no./total no.)	94.6% (70/74)[*]
95% CI for proportion[†]	(86.7%, 98.5%)

[*]One recipient with graft failure and re-transplant during the first 30 days was excluded.
[†]Clopper-Pearson exact confidence interval for a binomial proportion.

Incidence of severe ISHLT PGD (left or right ventricle) in the first 24 hours post-transplant:

Eight (8) of the 75 recipients of a donor heart preserved on the OCS Heart System experienced a severe ISHLT PGD. Thus, the incidence of severe ISHLT PGD (left or right ventricle) in the first 24 hours post-transplant was 10.7%, as summarized in Table 8.

Table 8: Incidence of Severe ISHLT PGD (Left or Right Ventricle) in the First 24 Hours Post-transplant - EXPAND Heart

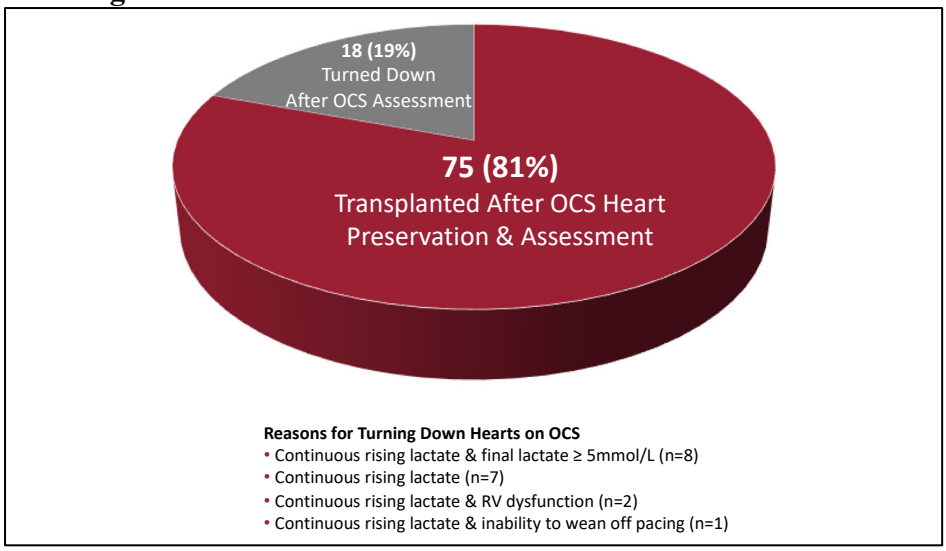
Incidence of severe ISHLT PGD (left or right ventricle) in the first 24 hours post-transplant (N=75)	
Proportion - % (no./total no.)	10.7% (8/75)
95% CI for proportion*	(4.7%, 19.9%)

*Clopper-Pearson exact confidence interval for a binomial proportion.

Rate of donor heart utilization:

A total of 93 donor hearts were preserved on the OCS Heart System, 75 of which were transplanted, giving a utilization rate of 80.6%, as shown in Figure 4.

Figure 4: Donor Heart Utilization Rate – EXPAND Heart



Incidence of HGRSAEs in the first 30 days:

The results of the HGRSAEs in the first 30 days are summarized in Table 9. Eleven (11) recipients experienced a total of 12 HGRSAEs, including one recipient who developed two HGRSAEs (severe LV PGD + re-transplantation). The incidence of HGRSAEs (i.e., number of HGRSAEs/subject) in the first 30 days was 0.16.

Table 9: HGRSAEs in the First 30 Days Post-transplant - EXPAND Heart

HGRSAEs in the first 30 days post-transplant (N=75)	
Number of HGRSAEs	12*
Moderate or severe PGD (LV or RV)	11
Severe LV PGD	6
Moderate LV PGD	3
RV PGD	2

HGRSAEs in the first 30 days post-transplant (N=75)	
Primary graft failure requiring re-transplantation	1
Incidence of HGRSAEs	0.16 (12/75)
95% CI[†]	(0.1, 0.2)

[*]One recipient developed two HGRSAEs (severe LV PGD + re-transplantation).
[†]Confidence interval calculated based on the t-distribution.

3. Adverse Events

The serious adverse events (SAEs) at 30 days observed during the EXPAND Heart study are summarized in Table 10. A total of 74.7% (56/75) of the recipients experienced an SAE, and 41.3% (31/75) experienced a cardiac SAE. No SAEs were adjudicated as having been device-related.

Table 10: Summary of SAEs at 30 Days - EXPAND Heart

System Organ Class	Preferred Term	Summary Statistic[*]	
		Recipients (N=75)	Events
Total		56 (74.7%)	105
Cardiac disorders		31 (41.3%)	38
	Arrhythmia	4 (5.3%)	4
	Arrhythmia supraventricular	1 (1.3%)	1
	Atrial fibrillation	5 (6.7%)	5
	Atrial flutter	1 (1.3%)	1
	Atrial tachycardia	1 (1.3%)	1
	Atrioventricular block	1 (1.3%)	1
	Bradycardia	1 (1.3%)	1
	Cardiac failure congestive	4 (5.3%)	4
	Cor pulmonale	2 (2.7%)	2
	Electromechanical dissociation	1 (1.3%)	1
	Left ventricular dysfunction	5 (6.7%)	5
	Left ventricular failure	1 (1.3%)	1
	Nodal rhythm	1 (1.3%)	1
	Pericardial effusion	5 (6.7%)	5
	Right ventricular dysfunction	4 (5.3%)	4
	Right ventricular failure	1 (1.3%)	1
General disorders and administration site conditions		1 (1.3%)	1
	Multi-organ failure	1 (1.3%)	1

System Organ Class	Preferred Term	Summary Statistic*	
		Recipients (N=75)	Events
Hepatobiliary disorders		1 (1.3%)	1
	Hepatic failure	1 (1.3%)	1
Immune system disorders		12 (16.0%)	12
	Heart transplant rejection	12 (16.0%)	12
Infections and infestations		4 (5.3%)	4
	Clostridial infection	1 (1.3%)	1
	H1N1 influenza	1 (1.3%)	1
	Pneumonia	1 (1.3%)	1
	Sepsis	1 (1.3%)	1
Injury, poisoning and procedural complications		9 (12.0%)	10
	Cardiac procedure complication	3 (4.0%)	3
	Heart injury	1 (1.3%)	1
	Operative hemorrhage	1 (1.3%)	1
	Post-operative thoracic procedure complication	1 (1.3%)	1
	Procedural complication - non-cardiac	2 (2.7%)	2
	Rectal laceration post-operative	1 (1.3%)	1
	Vascular pseudoaneurysm	1 (1.3%)	1
Metabolism and nutrition disorders		1 (1.3%)	1
	Fluid overload	1 (1.3%)	1
Nervous system disorders		6 (8.0%)	6
	Cerebrovascular accident	3 (4.0%)	3
	Convulsion	2 (2.7%)	2
	Vocal cord paralysis	1 (1.3%)	1
Psychiatric disorders		3 (4.0%)	3
	Delirium	3 (4.0%)	3
Renal and urinary disorders		12 (16.0%)	12
	Renal failure acute	10 (13.3%)	10
	Renal impairment	2 (2.7%)	2
Respiratory, thoracic and mediastinal disorders		14 (18.7%)	15
	Acute respiratory distress syndrome	1 (1.3%)	1

System Organ Class	Preferred Term	Summary Statistic*	
		Recipients (N=75)	Events
	Acute respiratory failure	2 (2.7%)	2
	Hydrothorax	1 (1.3%)	1
	Hypoxia	1 (1.3%)	1
	Pleural effusion	3 (4.0%)	3
	Respiratory distress	1 (1.3%)	1
	Respiratory failure	6 (8.0%)	6
Vascular disorders		2 (2.7%)	2
	Hemorrhage	1 (1.3%)	1
	Subclavian vein thrombosis	1 (1.3%)	1

*Number of recipients refers to the number of recipients with at least one SAE of the indicated type. Number of events refers to all events of the indicated type. Percentages are calculated based on the total number of recipients. For number of recipients, recipients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term.

4. Other Study Observations

Donor Heart Offer Refusals Prior to Acceptance into Study

UNOS manages the national system for matching patients on the waiting list with available donor hearts. Using the combination of donor and patient information, the UNOS computer system generates a "match run," a rank-order list of patients to be offered each donor organ. When a donor organ is turned down for a matched patient, it will be offered to the next matched patient on the list. Table 11 summarizes the donor match run data available from UNOS for the 93 donor hearts preserved on the OCS Heart System. These 93 hearts were refused for transplant by other centers an average of 66 times (median 29) before being offered to an EXPAND Heart study patient and accepted.

Table 11: Donor Heart Offer Refusals Prior to Acceptance into Study - EXPAND Heart

Donor Heart Offer Refusals by Other Centers	Summary Statistics (N = 93)
Number of refusals per donor heart - Mean ± SD	66 ± 90
Median number of refusals per donor heart	29
Range	0 - 379

Transplanted Donor Heart Preservation Characteristics

The transplanted donor heart preservation characteristics are summarized in Table 12. The mean cross-clamp time, OCS Heart System perfusion time, and total ischemic time were 380.7 ± 93.2, 278.6 ± 83.3, and 102.1 ± 22.6 minutes, respectively.

Table 12: Transplanted Donor Heart Preservation Characteristics – EXPAND Heart

Parameter	Summary Statistics (N=75)
Cross-clamp time (mins)*	
Mean ± SD	380.7 ± 93.2
Median	369
Range	173 - 682
OCS Heart System perfusion time (mins)	
Mean ± SD	278.6 ± 83.3
Median	276
Range	100 - 532
Total ischemic time (mins)†	
Mean ± SD	102.1 ± 22.6
Median	98
Range	65 - 168

*Cross-clamp time (i.e., out of body time) is the time from aortic cross-clamp application in the donor to the pulmonary artery cross-clamp removal in the recipient.

†Total ischemic time for hearts preserved by OCS Heart System is the cross-clamp time minus OCS Heart System perfusion time.

OCS Heart System Perfusion Parameters

The OCS Heart System perfusion parameters for the transplanted donor hearts are summarized in Table 13. The donor hearts were maintained within the recommended parameters on the OCS Heart System.

Table 13: OCS Heart System Perfusion Parameters – EXPAND Heart

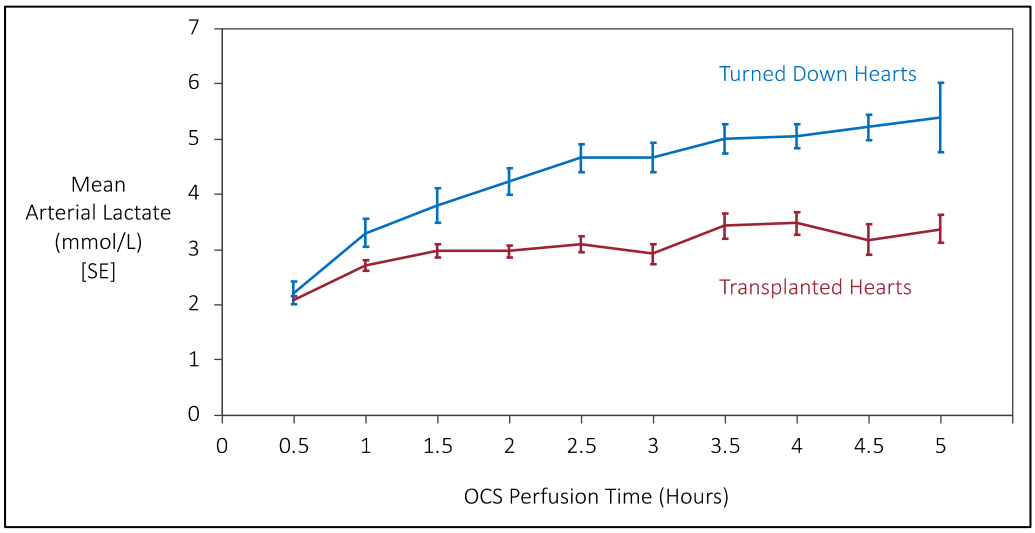
Parameter	Summary Statistics (N=75)
AOP (mmHg)	
Mean ± SD	81.2 ± 7.8
Median	81.4
Range	48 - 102
Coronary flow (L/min)	
Mean ± SD	0.76 ± 0.14
Median	0.785
Range	0.06 - 0.99
Arterial lactate (mmol/L) – Initial OCS instrumentation	
Mean ± SD	1.9 ± 0.63
Median	1.75

Parameter	Summary Statistics (N=75)
Range	0.93 - 3.80
Arterial lactate (mmol/L) – Final OCS instrumentation	
Mean ± SD	3.08 ± 0.95
Median	3.01
Range	0.55 - 4.97
Pump flow (L/min)	
Mean ± SD	1.13 ± 0.12
Median	1.12
Range	0.93 - 1.76
Heart rate (BPM)	
Mean ± SD	78.8 ± 2.5
Median	78.6
Range	74 - 87
Hematocrit (%)	N = 74
Mean ± SD	21.1 ± 3.6
Median	20.7
Range	16 – 33.0

Donor Heart Turndowns Following OCS Heart System Preservation

Of the 93 donor hearts instrumented on the OCS Heart System, 18 (matched to 16 recipients) did not meet transplantability criteria following preservation on the OCS Heart System as determined by the transplant surgeons due to unstable and rising lactate trends, as shown in Figure 5, as well as other clinical reasons (e.g., right ventricular disfunction and inability to regain sinus rhythm).

Figure 5: Mean Arterial Lactate Trend in Donor Hearts on OCS Heart System - EXPAND Heart



Mechanical Circulatory Support (MCS) Post-transplant

The use of MCS postoperatively in the EXPAND Heart study is summarized in Table 14. Twenty (20) of the 75 (26.7%) recipients required MCS postoperatively.

Table 14: Post-operative MCS Support – EXPAND Heart

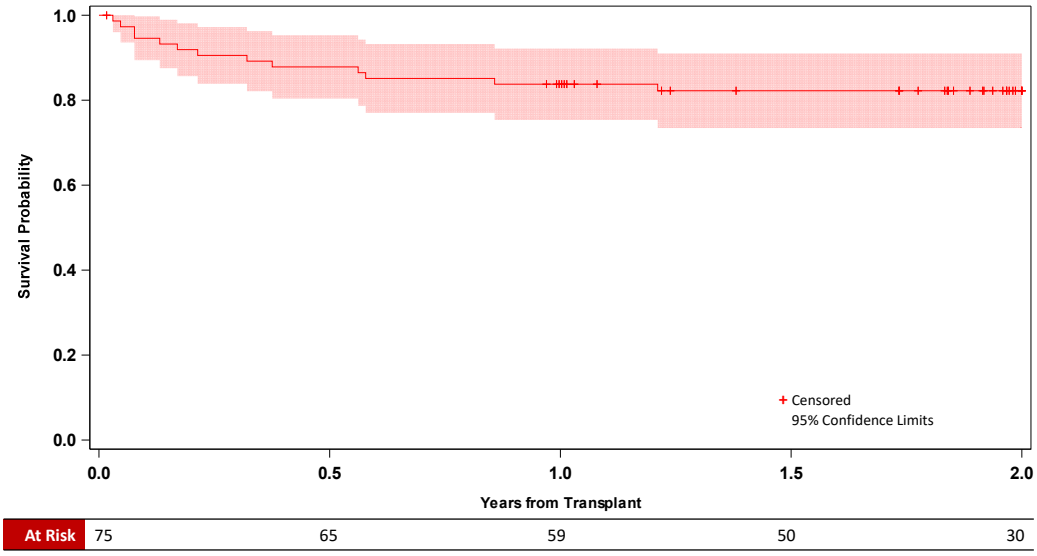
	Percentage of Patients* **(n/N)**	**Duration of Support†** **(hours)**
Mechanical circulatory support	26.7% (20/75)	
RVAD	2.7% (2/75)	219.12 ± 31.35
LVAD	2.7% (2/75)	139.0 ± 93.34
IABP	18.7% (14/75)	80.0 ± 63.20
ECMO	12.0% (9/75)	132.04 ± 97.09
BiVAD	0% (0/75)	-

*Percentages are calculated based on the number of transplanted recipients without missing data. A recipient may have more than one type of post-transplant support.
†The duration of support is the sum of the durations of all periods of support.

Longer-term Survival

All transplanted recipients in the EXPAND Heart study were followed through 2 years as of March 2020. There were a total of 13 deaths, including 4 cardiac-related deaths. The Kaplan-Meier analysis of the overall survival is shown in Figure 6. The overall survival rates were 83.8% at 1 year and 82.2% at 2 years.

Figure 6: Kaplan-Meier Analysis of Overall Survival - EXPAND Heart



5. Pediatric Extrapolation

In this premarket application, existing clinical data were not leveraged to support approval for a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conduction clinical studies covered by the regulation. The EXPAND Heart study involved 75 investigators of which none were full-time or part-time employees of the sponsor and no investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f), as described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study.
- Significant payment of other sorts.
- Proprietary interest in the product tested held by the investigator.
- Significant equity interest held by investigator in sponsor of covered study.

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

As part of the review of the PMA application, FDA also considered the supplemental clinical information summarized below.

XI.1 EXPAND Heart Continued Access Protocol (CAP) Study

A. Study Design

The EXPAND Heart CAP study was a single-arm, prospective, multicenter study carried out under IDE G140111, with a target enrollment of 75 transplanted recipients at 8 investigational sites.

1. Clinical Inclusion and Exclusion Criteria

   Donor heart inclusion and exclusion criteria for the EXPAND Heart CAP study were similar to those of the EXPAND Heart study except that the former:

   - Modified the ejection fraction inclusion criterion to be "left heart EF ≥40%, but ≤50% at time of acceptance of offer" and ejection fraction exclusion criterion to be "EF consistently <40%";
   - Clarified the definition of "significant coronary artery disease" as being <50% on angiogram;

   Recipient inclusion and exclusion criteria for the EXPAND Heart CAP study were the same as those of the EXPAND Heart study except that the former excluded patients with "chronic renal insufficiency" (CRI) requiring hemodialysis or renal replacement therapy, whereas the latter excluded all subjects with a diagnosis of CRI.

2. Follow-up Schedule

   Follow-up time points included day of transplant, 24 hours, discharge, 30 days, 6 months, and 1 year post transplant, and annually thereafter to 5 years post procedure. Pre- and post-implant assessments were the same as the EXPAND Heart study.

3. Clinical Endpoints

   The EXPAND Heart CAP study had the same primary endpoint and secondary endpoints as the EXPAND Heart study, but there was no hypothesis testing associated with the primary endpoint of the EXPAND Heart CAP study. Additionally, the EXPAND Heart CAP study included the following endpoints:

- Patient survival at 6 and 12 months post-transplant
- Incidence of primary graft failure requiring re-transplantation through 12 months post-transplant
- Duration of initial post-transplant ICU stay
- Duration of initial post-transplant hospital stay

B. Accountability of Study Cohort

At the time of database lock on August 26, 2020, 49 donor hearts were preserved using the OCS Heart System at 8 investigational sites in the U.S., of which 4 were turned down and 45 were transplanted. There was no female-to-male donor mismatch. Among the 45 recipients, 41 had reached the 30-day follow-up time point. This section summarizes the clinical results of these 41 recipients.

C. Study Population Demographics and Baseline Parameters

The inclusion criteria met by the transplanted donor hearts are summarized in Table 15. Many donor hearts exhibited multiple inclusion criteria. The demographics and baseline characteristics of the recipient patients are summarized in Table 16. Compared to the EXPAND Heart study, pre-transplantation ventricular assist device (VAD) use was substantially lower and pre-transplantation IABP use was more frequent in the EXPAND Heart CAP study.

Table 15: Inclusion Criteria Met by Transplanted Donor Hearts - EXPAND Heart CAP

Inclusion Criteria Met	Summary Statistics* (N=41)
Expected cross-clamp time ≥ 4hr	25 (61.0%)
Donor age ≥ 55	2 (4.9%)
Left ventricular hypertrophy	5 (12.2%)
Downtime ≥ 20 min	10 (24.4%)
LVEF 40% -50%	6 (14.6%)
Luminal irregularities	3 (7.3%)
Alcoholism	7 (17.1%)
History of carbon monoxide poisoning	0 (0.0%)
Diabetes	1 (2.4%)
Donor age 45-55 with no coronary catheterization data	0 (0.0%)
Donor hearts met single criterion	24 (58.5%)
Donor hearts met multiple criteria	17 (41.5%)

*Categorical measures – no. (%)

Table 16: Recipient Demographics and Baseline Characteristics - EXPAND Heart CAP

Demographics and Baseline Characteristics	Summary Statistics* (N=41)
Age (years)	52.1 ± 14.2
Age > 65	7 (17.1%)
Gender – male	32 (78.0 %)
BMI (kg/m^2)	29.4 ± 4.7
Race	
Asian	0 (0.0%)
Black or African American	12 (29.3%)
White	28 (68.3%)
Other	1 (2.4%)
Not provided	0 (0.0%)
History of mechanical circulatory support	28 (68.3%)
IABP	16 (39.0%)
LVAD	11 (26.8%)
RVAD	1 (2.4%)
BiVAD	0 (0.0%)
ECMO	2 (4.9%)
UNOS status	
Status IA (Status 1-3)	25 (61.0%)
Status IB (Status 4)	12 (29.3%)
Status II (Status 5 & 6)	4 (9.8%)
Primary etiology of heart failure diagnosis	
Ischemic cardiomyopathy	14 (34.1%)
Congenital heart disease	3 (7.3%)
Restrictive cardiomyopathy	0 (0.0%)
Non-ischemic cardiomyopathy	15 (36.6%)
Dilated cardiomyopathy	7 (17.1%)
Other	2 (4.9%)
Renal dysfunction	1 (2.4%)
Percent PRA - mean (range)	6.6% (0-79%)

*Continuous measures - Mean ± SD; categorical measures – no. (%)

D. Safety and Effectiveness Results

1. Primary Endpoint

The analysis of the primary endpoint is summarized in Table 17. All 41 recipients were alive at 30 days post-transplant and one (1) patient had severe PGD in the first 24 hours post-transplant.

Table 17: Primary Endpoint Result - EXPAND Heart CAP

Patient survival at 30 days post-transplant and absence of severe PGD (left or right ventricle) in the first 24 hours post-transplant (N=41)	
Proportion - % (no./total no.)[*]	97.6% (40/41)
95% CI for proportion[†]	(87.1%, 99.9%)

[*]Simple proportion.
[†]Clopper-Pearson exact confidence interval for a binomial proportion.

2. Secondary Endpoints

Patient/graft survival at 30 days post-transplant:

The result of patient/graft survival at 30 days post-transplant is summarized in Table 18. The patient/graft survival rate was 100% at 30 days post-transplant.

Table 18: Patient/Graft Survival at 30 Days Post-transplant - EXPAND Heart CAP

Patient survival at 30 days post-transplant (N=41)	
Proportion - % (no./total no.)	100% (41/41)
95% CI for proportion[*]	(91.4%, 100%)

[*]Clopper-Pearson exact confidence interval for a binomial proportion.

Incidence of severe ISHLT PGD (left or right ventricle) in the first 24 hours post-transplant:

One (1) of the 41 recipients of a donor heart preserved on the OCS Heart System experienced a severe ISHLT PGD. Thus, the incidence of severe ISHLT PGD (left or right ventricle) in the first 24 hours post-transplant was 2.4%, as summarized in Table 19.

Table 19: Incidence of Severe ISHLT PGD (Left or Right Ventricle) in the First 24 Hours Post-transplant - EXPAND Heart CAP

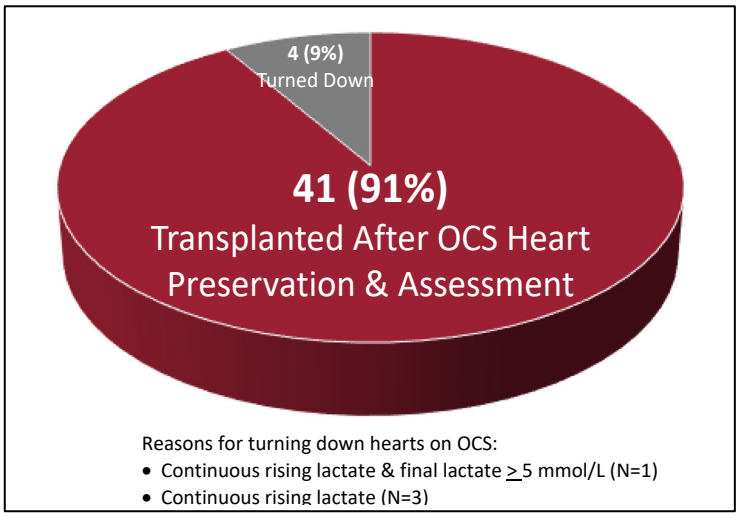
Incidence of severe ISHLT PGD (left or right ventricle) in the first 24 hours post-transplant (N=41)	
Proportion - % (no./total no.)	2.4% (1/41)
95% CI for proportion[*]	(0.1%, 12.9%)

[*]Clopper-Pearson exact confidence interval for a binomial proportion.

Rate of donor heart utilization:

Forty-one (41) of the 45 donor hearts instrumented on the OCS Heart System were transplanted, giving a utilization rate of 91.1%, as shown in Figure 7.

Figure 7: Donor Heart Utilization Rate – EXPAND Heart CAP



Incidence of HGRSAEs in the first 30 days:

The results of the HGRSAEs in the first 30 days are summarized in Table 20. Seven (7) recipients experienced a total of 7 HGRSAEs. The incidence of HGRSAEs in the first 30 days was 0.17.

Table 20: HGRSAEs in the First 30 Days Post-transplant - EXPAND Heart CAP

HGRSAEs in the first 30 days post-transplant (N=41)	
Number of HGRSAEs	7
Moderate or severe PGD (LV or RV)	7
Severe LV PGD	1
Moderate LV PGD	6
RV PGD	0
Primary graft failure requiring re-transplantation	0
Incidence of HGRSAEs	0.17 (7/41)
95% CI*	(0.1, 0.3)

*Confidence interval calculated based on the t-distribution.

3. Adverse Events

The SAEs at 30 days observed during the EXPAND Heart CAP study are summarized in Table 21. A total of 65.9% (27/41) of the recipients experienced an SAE, and 31.7% (13/41) experienced a cardiac SAE. No SAEs were adjudicated as having been device-related.

Table 21: Summary of SAEs at 30 Days - EXPAND Heart CAP

System Organ Class	Preferred Term	Summary Statistic*	
		Recipients (N=41)	Events
Total		27 (65.9%)	54
Blood and lymphatic system disorders		1 (2.4%)	1
	Anemia	1 (2.4%)	1
Cardiac disorders		13 (31.7%)	16
	Atrial fibrillation	3 (7.3%)	3
	Atrioventricular block	2 (4.9%)	2
	Intrapericardial thrombosis	1 (2.4%)	1
	Left ventricular dysfunction	3 (7.3%)	3
	Pericardial hemorrhage	1 (2.4%)	1
	Right ventricular dysfunction	3 (7.3%)	3
	Sinus bradycardia	1 (2.4%)	1
	Ventricular dysfunction	2 (4.9%)	2
Immune system disorders		4 (9.8%)	4
	Heart transplant rejection	4 (9.8%)	4
Infections and infestations		3 (7.3%)	3
	Bacteremia	1 (2.4%)	1
	Pneumonia	2 (4.9%)	2
Injury, poisoning and procedural complications		1 (2.4%)	1
	Vena cava injury	1 (2.4%)	1
Metabolism and nutrition disorders		2 (4.9%)	2
	Dehydration	1 (2.4%)	1
	Fluid overload	1 (2.4%)	1
Nervous system disorders		3 (7.3%)	3
	Cerebrovascular accident	1 (2.4%)	1
	Hemorrhagic stroke	1 (2.4%)	1
	Neuralgia	1 (2.4%)	1
Psychiatric disorders		2 (4.9%)	2
	Delirium	2 (4.9%)	2
Renal and urinary disorders		10 (24.4%)	10
	Renal failure acute	9 (22.0%)	9

System Organ Class	Preferred Term	Summary Statistic*	
		Recipients (N=41)	Events
	Renal impairment	1 (2.4%)	1
Respiratory, thoracic and mediastinal disorders		4 (9.8%)	6
	Bronchial secretion retention	1 (2.4%)	1
	Pleural effusion	3 (7.3%)	3
	Pulmonary oedema	1 (2.4%)	1
	Respiratory failure	1 (2.4%)	1
Vascular disorders		5 (12.2%)	6
	Aortic dissection	1 (2.4%)	1
	Hematoma	1 (2.4%)	1
	Hemorrhage	1 (2.4%)	1
	Hypotension	1 (2.4%)	1
	Orthostatic hypotension	2 (4.9%)	2

*Number of recipients refers to the number of recipients with at least one SAE of the indicated type. Number of events refers to all events of the indicated type. Percentages are calculated based on the total number of recipients. For number of recipients, recipients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term.

4. Other Study Observations

Donor Heart Offer Refusals Prior to Acceptance into Study

Table 22 summarizes the donor match run data available from UNOS for the 45 donor hearts preserved on the OCS Heart System. These 45 hearts were refused for transplant by other centers an average of 48 times (median 12) before acceptance into the EXPAND Heart CAP study.

Table 22: Donor Heart Offer Refusals Prior to Acceptance into Study - EXPAND Heart CAP

Donor Heart Offer Refusals by Other Centers	Summary Statistics (N = 45)
Number of refusals per donor heart - Mean ± SD	48 ± 93
Median number of refusals per donor heart	12
Range	0 - 480

Transplanted Donor Heart Preservation Characteristics

The transplanted donor heart preservation characteristics are summarized in Table 23. The mean cross-clamp time, OCS Heart System perfusion time, and total ischemic time were 382.3 ± 87.9, 278.3 ± 77.2, and 104.0 ± 22.2 minutes, respectively.

Table 23: Transplanted Donor Heart Preservation Characteristics – EXPAND Heart CAP

Parameter	Summary Statistics (N=41)
Cross-clamp time (mins)*	
Mean ± SD	382.3 ± 87.9
Median	385
Range	253 - 585
OCS Heart System perfusion time (mins)	
Mean ± SD	278.3 ± 77.2
Median	278
Range	158 - 440
Total ischemic time (mins)†	
Mean ± SD	104.0 ± 22.2
Median	98
Range	69 - 189

*Cross-clamp time (i.e., out of body time) is the time from aortic cross-clamp application in the donor to the pulmonary artery cross-clamp removal in the recipient.
†Total ischemic time for hearts preserved by OCS Heart System is the cross-clamp time minus OCS Heart System perfusion time.

OCS Heart System Perfusion Parameters

The OCS Heart System perfusion parameters for the transplanted donor hearts are summarized in Table 24.

Table 24: OCS Heart System Perfusion Parameters – EXPAND Heart CAP

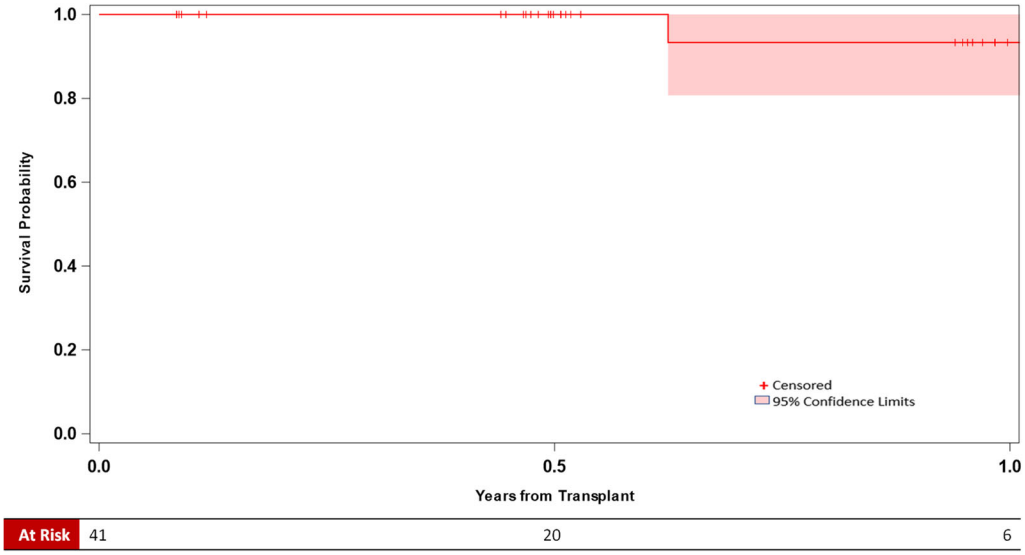
Parameter	Summary Statistics (N=41)
AOP (mmHg)	
Mean ± SD	77.4 ± 8.5
Median	79.3
Range	52 – 96
Coronary flow (L/min)	
Mean ± SD	0.73 ± 0.11

Parameter	Summary Statistics (N=41)
Median	0.75
Range	0.32 - 0.92
Arterial lactate (mmol/L) – Initial OCS instrumentation	
Mean ± SD	1.8 ± 0.85
Median	1.7
Range	0.67 – 5.70
Arterial lactate (mmol/L) – Final OCS instrumentation	
Mean ± SD	2.9 ± 1.26
Median	2.6
Range	1.28 – 7.59
Pump flow (L/min)	
Mean ± SD	1.10 ± 0.11
Median	1.10
Range	0.89 - 1.42
Heart Rate (BPM)	
Mean ± SD	78.7 ± 1.4
Median	78.5
Range	77 - 85
Hematocrit (%)	
Mean ± SD	20.0 ± 3.4
Median	19.1
Range	15 – 32

Longer-term Survival

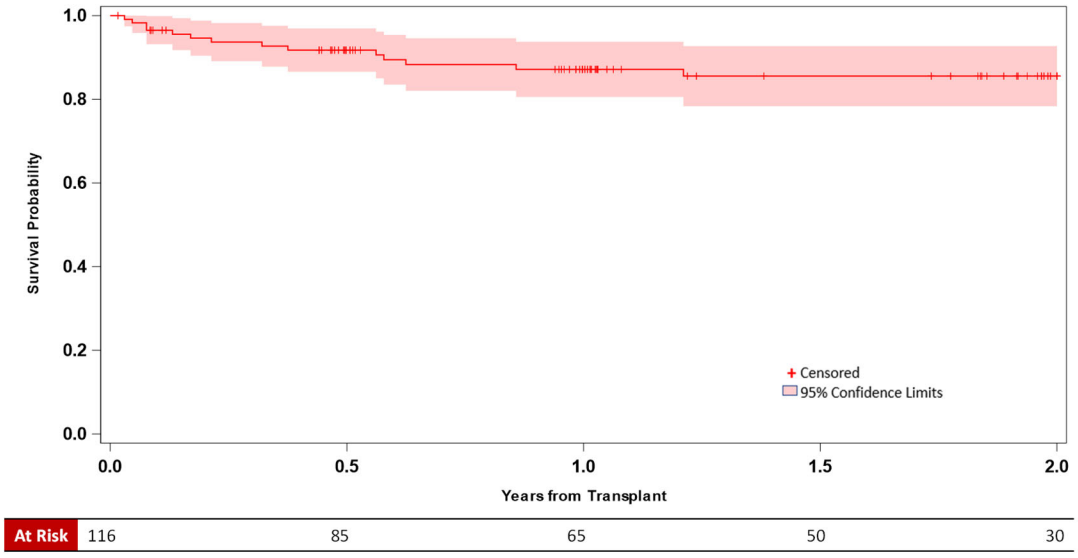
The Kaplan-Meier analysis of the overall survival is shown in Figure 8. The Kaplan-Meier estimates of the overall survival rates were 100% at 6 months and 93.3% at 1 year.

Figure 8: Kaplan-Meier Analysis of Overall Survival - EXPAND Heart CAP



A *post hoc* Kaplan-Meier analysis of the overall survival for the pooled EXPAND Heart and EXPAND Heart CAP recipients is shown in Figure 9. The Kaplan-Meier estimates of the overall survival rates were 91.7% at 6 months and 87.2% at 1 year.

Figure 9: Kaplan-Meier Analysis of Overall Survival - EXPAND Heart + EXPAND Heart CAP



XI.2 PROCEED II Trial

The PROCEED II trial was a historical pivotal study preceding the EXPAND Heart study. It was carried out using an earlier design iteration of the OCS Heart System, with an aim to

evaluate the safety and effectiveness of the OCS Heart System in preserving standard criteria donor hearts for transplantation (denoted as "OCS arm").

A. Study Design

The PROCEED II trial was a prospective, randomized (1:1), open-label, multicenter study conducted under IDE G060127, with a target sample size of 128. The control arm was donor heart preservation using standard-of-care (SOC) cold cardioplegic storage (denoted as "SOC arm").

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the PROCEED II trial was limited to donor hearts and transplant recipient patients that met the following:

   Donor heart prior to preservation:

   - < 60 years old
   - Mean arterial blood pressure > 60 mmHg at the time of final heart assessment
   - Satisfactory echocardiography assessment defined as:
     - Ejection fraction > 40%
     - Absence of severe segmental wall motion abnormalities
     - Absence of left ventricular hypertrophy (Inter Ventricular Septum (IVS) and Posterior Wall Thickness (PWT) < 1.3 cm)
     - Absence of valve abnormalities (trace to mild valvular regurgitation is acceptable)

   Recipient - day of transplant:

   - Registered primary heart transplant candidate
   - >18 years old
   - Signed written informed consent document and authorization to use and disclose protected health information

   Donor hearts and transplant recipient patients were not permitted to enroll in the study if they met any of the following exclusion criteria:

   Donor heart prior to preservation:

   - Abnormal coronary angiogram defined as > 50% stenosis, requiring coronary bypass
   - Donor-to-recipient body weight ratio of < 0.6
   - Vasoactive medicinal support at time of final heart assessment, including, but not limited to:
     - Dopamine > 10 ug/kg/min
     - Dobutamine > 10 ug/kg/min
     - Milrinone > 0.3 ug/kg/min
     - Epinephrine > 0.03 ug/kg/min

- Norepinephrine > 0.03 ug/kg/min
- Any bolus dose of the above prior to explants that would result in exceeding the above stated criteria

- Presence of any exclusion criterion based on the standard practice of the investigational site

Recipient - day of transplant:

- > 4 previous sternotomies
- Chronic renal failure as defined by chronic serum creatinine >3.0 mg/dL for more than 2 weeks and/or requiring hemodialysis (except for hemodialysis or hemofiltration for fluid overload)
- Ventilator dependence at the time of transplant
- Use of a VAD for > 30 days and the presence of any of the following: systemic sepsis, intracranial hemorrhage or heparin induced thrombocytopenia
- Panel reactive antibodies > 40% with a positive prospective cross match and/or virtual cross match
- Use of any investigational drug or device, other than OCS, during the study
- Simultaneous transplant of non-heart allograft, except for concurrent kidney transplant

2. Follow-up Schedule

Follow-up time points included day of transplant, 2 days, 7 days, 14 days, 21 days, 28 days, discharge, and 30 days. Pre- and post-implant assessments included medical and cardiac history and functional assessments. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

The primary endpoint was patient survival at 30 days post-transplant with the originally transplanted heart and without any MCS device:

$$H_0: \pi_{OCS} < \pi_{SOC} - \delta$$
$$H_0: \pi_{OCS} \geq \pi_{SOC} - \delta$$

where π_{OCS} and π_{SOC} are the respective proportions of patients surviving at 30 days in the test arm and control arm and δ is the non-inferiority margin, which was prespecified to be 0.10. If non-inferiority was demonstrated, the protocol allowed for superiority testing.

The secondary endpoints included the following, all of which had a non-inferiority hypothesis:

- Incidence of cardiac graft-related SAEs at 30 days (non-inferiority margin: 0.1).
- Rejection at 30 days (i.e., incidence of biopsy proven ISHLT grade 2R (moderate) or 3R (severe) acute rejection on any of the surveillance endomyocardial biopsies or

clinically symptomatic rejection requiring augmentation of immunosuppressive therapy during the 30-day follow-up period; non-inferiority margin: 0.1).
- Median length of ICU stay (non-inferiority margin: 12 hours).

B. Accountability of Study Patients

Patients in the PROCEED II trial were enrolled between March 21, 2009 and September 16, 2013 at 11 investigational sites in the U.S., U.K., Italy, and France. The clinical data summarized herein reflected data collected through October 25, 2013.

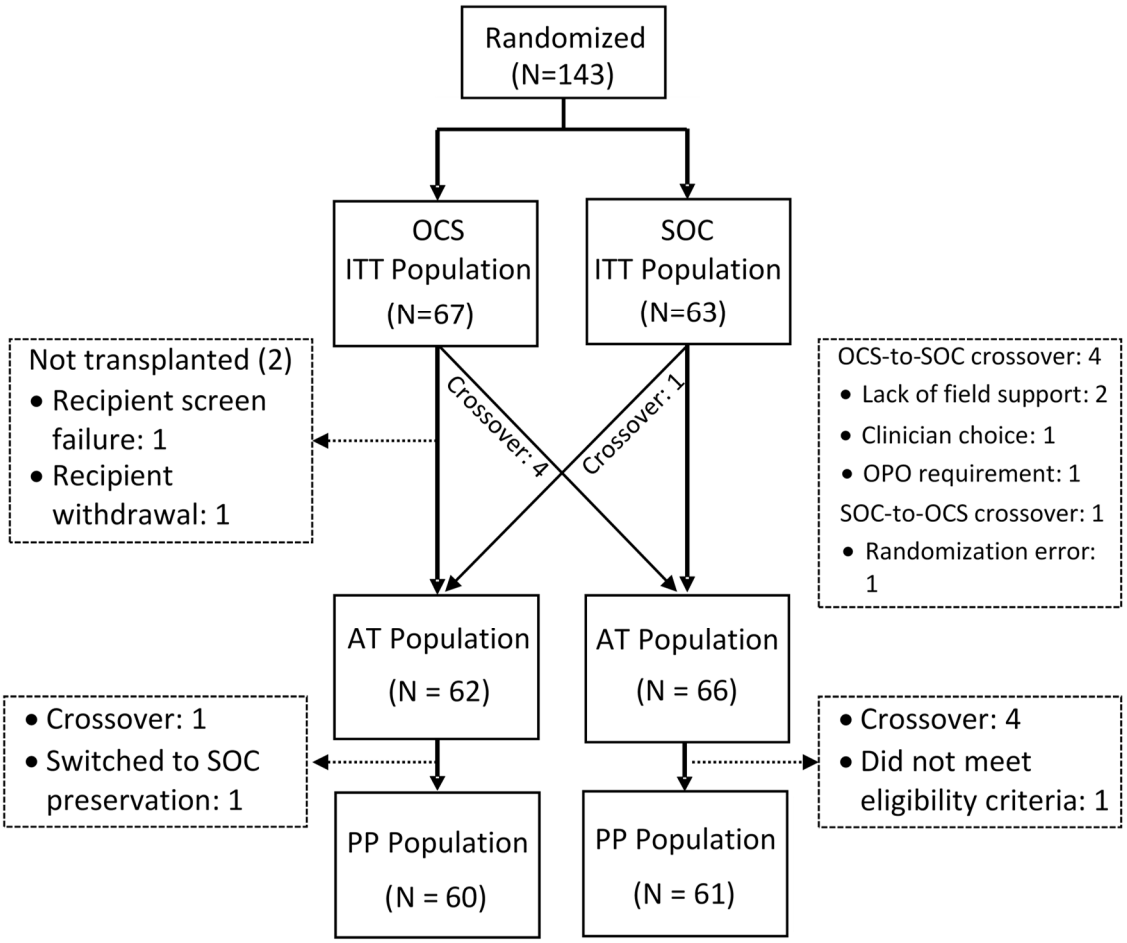
A total of 143 patients were initially screened and randomized, including 74 randomized to the OCS arm and 69 to the SOC arm. Thirteen (13) of the 143 patients failed secondary screening/eligibility, including 7 in the OCS arm and 6 in the SOC arm, which led to 67 and 63 patients in the OCS and SOC arms, respectively. Five (5) donor hearts preserved using the OCS Heart System were turned down compared to zero (0) for donor hearts preserved using the cold storage method. Twelve (12) male recipients each in the OCS arm and SOC arm received a heart from a female donor.

There were three different analysis populations defined in the protocol: Intention-to-Treat (ITT), As Treated (AT), and Per Protocol (PP), as summarized in Table 25 and Figure 10. The primary analysis was the PP analysis. All secondary endpoints were analyzed using the AT population.

Table 25: Analysis Populations

Analysis Population	Definition	Number of Patients	
		OCS	SOC
Intention-To-Treat (ITT)	All randomized patients for whom it was determined at the donor site that there was a matching and eligible heart.	67	63
As Treated (AT)	All ITT patients who received a donor heart preserved by either the OCS or SOC technique, regardless of whether or not the patient received a donor heart according to the randomization assignment.	62	66
Per Protocol (PP)	All AT patients who were transplanted according to their randomization assignments and had no major protocol deviations.	60	61

Figure 10: Patient Population Flowchart



C. Study Population Demographics and Baseline Parameters

The demographics and baseline characteristics of the donors and recipient patients are summarized in Table 26 and Table 27, respectively, which were generally similar between the two study arms.

Table 26: Donor Demographics and Baseline Characteristics – PROCEED II Trial (PP Population)

Demographics and Baseline Characteristics	Summary Statistics*	
	OCS Arm (N=60)	SOC Arm (N=61)
Age (years)	36.4 ± 12.8	34.2 ± 12.3
≥ 55	2 (3.3%)	3 (4.9%)
Gender – male	40 (66.7%)	44 (72.1%)
BMI (kg/m^2)	27.6 ± 5.5	26.0 ± 4.9
LVEF (%)	60.8 ± 5.8	62.1 ± 6.1
Cause of death		

Anoxia	14 (23.3%)	13 (21.3%)
Stroke/CVA	17 (28.3%)	16 (26.2%)
Head trauma	26 (43.3%)	28 (45.9%)
Other	3 (5.0%)	4 (6.6%)

*Continuous measures - Mean ± SD; categorical measures – no. (%)

Table 27: Recipient Demographics and Baseline Characteristics – PROCEED II Trial (PP Population)

Demographics and Baseline Characteristics	Summary Statistics*	
	OCS Arm (N=60)	SOC Arm (N=61)
Age (years)	53.1 ± 12.4	54.4 ± 13.7
> 65	11 (18.3%)	16 (26.2%)
Gender – male	50 (83.3%)	43 (70.5%)
BMI (kg/m^2)	26.3 ± 5.3	24.2 ± 4.2
Clinical history of diabetes	16 (26.7%)	15 (24.6%)
On VAD	17 (28.3%)	14 (23.0%)
Diagnosis of cardiomyopathy		
Ischemic	22 (36.7%)	18 (29.5%)
Idiopathic	6 (10.0%)	9 (14.8%)
Dilated cardiomyopathy	20 (33.3%)	20 (32.8%)
Congenital heart disease	1 (1.7%)	1 (1.6%)
Restrictive	2 (3.3%)	4 (6.6%)
Other	9 (15.0%)	9 (14.8%)
UNOS status		
IA	42 (70.0%)	48 (78.7%)
IB	8 (13.3%)	6 (9.8%)
II	10 (16.7%)	7 (11.5%)

*Continuous measures - Mean ± SD; categorical measures – no. (%)

D. Safety and Effectiveness Results

1. Primary Endpoint

The primary endpoint results for various analysis populations are summarized in Table 28. For the PP population, 93.3% of the patients in the OCS arm were alive at 30 days post-transplant with the originally transplanted heart and without any MCS device compared to 96.7% in the SOC arm. Since the 95% upper confidence bound for the difference in the primary endpoint event rate between the two study arms was less than 10%, the trial met its primary endpoint. In addition, the primary endpoint was met for the AT and ITT populations. Superiority was not demonstrated, and the numerical results favored the SOC arm.

Table 28: Primary Endpoint Results – PROCEED II

Analysis Population	Primary Endpoint Event Rate*		Difference (SOC-OCS)	95% Upper Confidence Bound of Difference	Non-inferiority Criterion†
	OCS	SOC			
PP	93.3% (56/60)	96.7% (59/61)	3.4%	9.9%	Pass
AT	93.5% (58/62)	97.0% (64/66)	3.5%	9.6%	Pass
ITT‡	94.0% (63/67)	96.8% (61/63)	2.8%	8.8%	Pass

*Event rate - % (no./total no.).
†Non-inferiority margin: 10%.
Missing values were imputed with multiple imputation. The logistic regression method of imputation was used with terms for treatment, age, and gender.

2. Secondary Endpoints

Incidence of Cardiac Graft-Related SAEs at 30 Days:

The incidences of cardiac graft-related SAEs at 30 days are summarized in Table 29. Eight (8; 12.9%) patients in the OCS arm and 9 (13.6%) in the SOC arm experienced a cardiac graft-related SAE. The 95% upper confidence bound of the difference in the incidence between the OCS arm and SOC arm (OCS - SOC) was 9.1%, which was less than that the pre-specified non-inferiority margin of 10%. As such, the study demonstrated non-inferiority of the OCS Heart System preservation to cold storage preservation in the incidence of cardiac graft-related SAEs at 30 days post-transplant.

Table 29: Cardiac Graft-Related SAEs – PROCEED II (AT Population)

Statistic	OCS (N=62)	SOC (N=66)
Number of cardiac graft-related SAEs	8	9
Incidence of cardiac graft-related SAEs	12.9% (8/62)	13.6% (9/66)
Difference in incidence between arms	-0.7%	
95% upper confidence bound of difference*	9.1%	
Non-inferiority margin	10%	
Non-inferiority criterion	Pass	

*Calculated based on the normal approximation

Rejection at 30 Days:

The incidences of graft rejections during the 30-day follow-up period are summarized in Table 30. Eleven (11; 17.7%) patients in the OCS arm and 9 (13.6%) in the SOC arm experienced moderate acute graft rejection requiring augmentation of immunosuppressive therapy. The 95% upper confidence bound of the difference in graft rejection rate at 30 days

between the OCS arm and SOC arm (OCS - SOC) was 14.7%, which was greater than the pre-specified non-inferiority margin of 10%. As such, the study failed to demonstrate non-inferiority of graft rejection post-transplant.

Table 30: Graft Rejection at 30 Days – PROCEED II (AT Population)

Statistic	OCS (N=62)	SOC (N=66)
Number of rejections	11	9
Grade 3R rejection	0	0
Grade 2R rejection	11	9
Clinically symptomatic rejection	0	0
Incidence of rejections	17.7% (11/62)	13.6% (9/66)
Difference between arms	4.1%	
95% upper confidence bound of difference	14.7%	
Non-inferiority margin	10%	
Non-inferiority criterion	Failed	

Median Length of ICU Stay:

The length of initial ICU stay data are summarized in Table 31. The median length of the initial ICU stay was 147.1 hours for the OCS arm and 137.1 hours for the SOC arm. The 95% upper confidence bound of the difference in median (OCS - SOC) was 37.7 hours, which was greater than the pre-specified non-inferiority margin of 12 hours. Thus, statistical non-inferiority was not observed.

Table 31: Median Length of ICU Stay – PROCEED II (AT Population)

Statistic (hours)	OCS (N=62)	SOC (N=66)
Mean (SD)	234.2 (349.0)	161. 3 (92.1)
Median	147.1	137.1
Difference in median between arms	10.0	
95% upper confidence bound of difference*	37.7	
Non-inferiority margin	12	
Non-inferiority criterion	Failed	

*Calculated based on the normal approximation to the Wilcoxon rank sum test statistic.

3. Adverse Events

The SAEs at 30 days observed during the PROCEED II trial are summarized in Table 32. A total of 46.8% (29/62) of the recipients in the OCS arm and 34.8% (23/66) in the SOC arm experienced an SAE.

Table 32: Summary of SAEs at 30 Days – PROCEED II (AT Population)

System Organ Class	Preferred Term	Summary Statistic*	
		OCS (N=62)	SOC (N=66)
Total		29 (46.8%)	23 (34.8%)
Blood and lymphatic system disorders		3 (4.8%)	1 (1.5%)
	Coagulopathy	3 (4.8%)	0 (0.0%)
	Thrombocytopenia	0 (0.0%)	1 (1.5%)
Cardiac disorders		13 (21.0%)	9 (13.6%)
	Cardiac arrest	1 (1.6%)	1 (1.5%)
	Intrapericardial thrombosis	0 (0.0%)	1 (1.5%)
	Left ventricular dysfunction	0 (0.0%)	2 (3.0%)
	Pericardial effusion	3 (4.8%)	0 (0.0%)
	Right ventricular dysfunction	2 (3.2%)	6 (9.1%)
	Tricuspid valve incompetence	3 (4.8%)	0 (0.0%)
	Ventricular dysfunction	4 (6.5%)	1 (1.5%)
Gastrointestinal disorders		0 (0.0%)	1 (1.5%)
	Pancreatitis acute	0 (0.0%)	1 (1.5%)
General disorders and administration site conditions		1 (1.6%)	1 (1.5%)
	Catheter site inflammation	1 (1.6%)	0 (0.0%)
	Influenza like illness	0 (0.0%)	1 (1.5%)
Hepatobiliary disorders		1 (1.6%)	0 (0.0%)
	Cholecystitis	1 (1.6%)	0 (0.0%)
Immune system disorders		1 (1.6%)	1 (1.5%)
	Heart transplant rejection	1 (1.6%)	1 (1.5%)
Infections and infestations		4 (6.5%)	1 (1.5%)
	Adenoviral upper respiratory infection	1 (1.6%)	0 (0.0%)
	Lobar pneumonia	1 (1.6%)	0 (0.0%)
	Perirectal abscess	0 (0.0%)	1 (1.5%)
	Septic shock	1 (1.6%)	0 (0.0%)
	Urosepsis	1 (1.6%)	0 (0.0%)
Injury, poisoning and procedural complications		7 (11.3%)	7 (10.6%)

System Organ Class	Preferred Term	Summary Statistic*	
		OCS (N=62)	SOC (N=66)
	Deep vein thrombosis Postoperative	1 (1.6%)	0 (0.0%)
	Operative hemorrhage	1 (1.6%)	1 (1.5%)
	Post procedural hemorrhage	6 (9.7%)	6 (9.1%)
Investigations		1 (1.6%)	1 (1.5%)
	Cardiac Output Decreased	0 (0.0%)	1 (1.5%)
	Pulmonary Arterial Wedge Pressure Increased	1 (1.6%)	0 (0.0%)
Metabolism and nutrition disorders		1 (1.6%)	0 (0.0%)
	Hypovolemia	1 (1.6%)	0 (0.0%)
Nervous system disorders		1 (1.6%)	3 (4.5%)
	Cerebral hematoma	0 (0.0%)	1 (1.5%)
	Dizziness	1 (1.6%)	0 (0.0%)
	Paresis	0 (0.0%)	1 (1.5%)
	Subarachnoid hemorrhage	0 (0.0%)	1 (1.5%)
Renal and urinary disorders		4 (6.5%)	3 (4.5%)
	Oliguria	0 (0.0%)	1 (1.5%)
	Renal failure	2 (3.2%)	0 (0.0%)
	Renal failure acute	2 (3.2%)	2 (3.0%)
Respiratory, thoracic and mediastinal disorders		7 (11.3%)	3 (4.5%)
	Pleural effusion	0 (0.0%)	1 (1.5%)
	Pneumothorax	0 (0.0%)	1 (1.5%)
	Pulmonary oedema	1 (1.6%)	0 (0.0%)
	Respiratory distress	2 (3.2%)	0 (0.0%)
	Respiratory failure	4 (6.5%)	1 (1.5%)
Vascular disorders		3 (4.8%)	1 (1.5%)
	Hemorrhage	1 (1.6%)	1 (1.5%)
	Hypotension	1 (1.6%)	0 (0.0%)
	Peripheral artery aneurysm	1 (1.6%)	0 (0.0%)

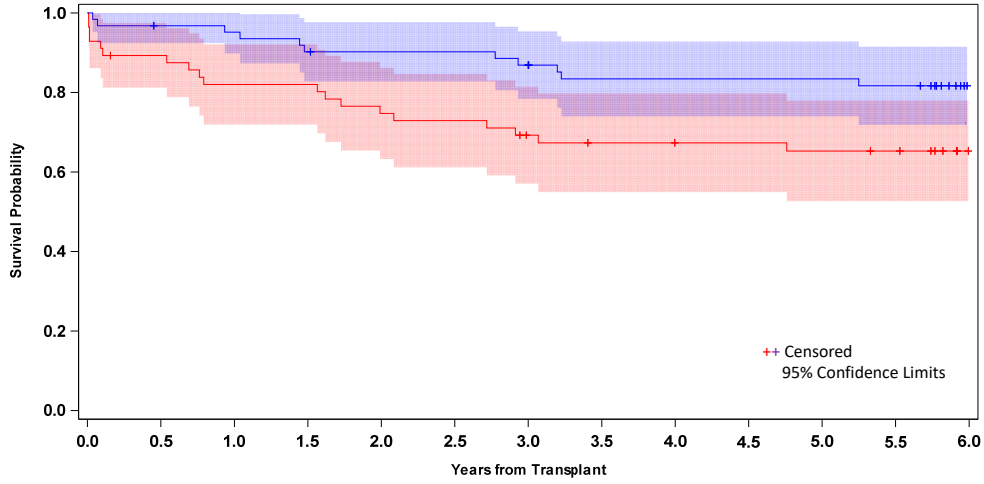
*No. (%) - Number of recipients with at least one SAE of the indicated type (percentages calculated based on the total number of recipients). Recipients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term.

4. Other Study Observations

Long-term Survival

A *post hoc* Kaplan-Meier analysis of long-term survival based on data from the UNOS heart transplant registry is shown in Figure 11 for recipients treated in the U.S. only, which demonstrated a lower overall survival trend in the OCS arm (82.0% at 1 year and 74.7% at 2 years) compared to the SOC arm (95.1% at 1 year and 90.2% at 2 years).

Figure 11: Kaplan-Meier Analysis of Overall Survival – PROCEED II (AT Population; U.S. Subgroup)



OCS	56	49	45	45	41	40	36	34	33	33	32	31	23
SOC	62	59	58	55	54	54	51	48	48	48	48	47	37

XI.3 Clinicopathologic Analysis of Turned-Down Donor Hearts

In the three clinical studies summarized above, a total of 27 donor hearts were turned down after being preserved using the OCS Heart System, including 18 in the EXPAND Heart study, 4 in the EXPAND Heart CAP study, and 5 in the PROCEED II study. The pathology core laboratory reports were available for 26 of these turned-down hearts, which indicated findings of acute diffuse or multifocal myocardial damage in 23 hearts despite that these hearts had stable antemortem hemodynamics, normal (or essentially normal) cardiac anatomy, and normal ventricular function by echocardiography. It is unknown whether the injury was due to use of the OCS Heart System.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on April 6, 2021, the Circulatory System Devices Panel voted 9 (yes)-7(no)-2(abstain) that there is reasonable assurance the device is safe, 10-6-2 that there is reasonable assurance that the device is effective, and 12-5-1 that the benefits of the device

outweigh the risks in patients who meet the criteria specified in the proposed indication. Additional information on the Advisory Panel can be found at the following website: https://www.fda.gov/advisory-committees/advisory-committee-calendar/april-6-2021-circulatory-system-devices-panel-medical-devices-advisory-committee-meeting.

B. FDA's Post-Panel Action

FDA worked interactively with the applicant to formulate the labeling and post approval study protocols to address the recommendations by the Panel and the FDA.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The EXPAND Heart pivotal study evaluated the preservation of "non-standard criteria" DBD hearts using the OCS Heart System. In the study, 88.0% of the recipients of a donor heart were alive at 30 days post-transplant without severe PGD (left or right ventricle) in the first 24 hours post-transplant, with a 95% lower confidence bound of 78.4%, which is greater than the pre-specified performance goal of 65% ($p < 0.0001$). Thus, the study met the primary endpoint. This result was confirmed in the EXPAND Heart CAP study.

The overall survival rate among transplanted patients in the EXPAND Heart study was 83.8% at 1 year and 82.2% at 2 years. However, in the randomized controlled PROCEED II trial evaluating the preservation of "standard criteria" DBD hearts using the OCS Heart System, the survival rate in the OCS arm was 82.0% at 1 year and 74.7% at 2 years compared to 95.1% at 1 year and 90.2% at 2 years in the SOC arm, based on available data captured in the UNOS heart transplant registry. These results suggest that the OCS Heart System should not be used on donor hearts that can be preserved using the cold static cardioplegic preservation.

In the EXPAND Heart study, the median number of turndowns of the donor hearts by other transplant centers was 29 before they were accepted into the study, compared to the reported median number of turndowns of 2 based on the 2007-2014 UNOS heart transplant registry data (Baran, et al. 2019). This suggests that these donor hearts would have had a higher likelihood of not being utilized outside of the study. Among the donor hearts preserved using the OCS Heart System in the EXPAND Heart Study, 80.6% of them were transplanted. Thus, use of the OCS Heart System on DBD hearts deemed unsuitable for preservation using the cold storage method could potentially expand the availability of donor hearts in the U.S.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in clinical studies conducted to support PMA approval as described above.

In the EXPAND Heart study, the safety of the device was primarily assessed through the endpoint of HGRSAEs. The number of HGRSAEs per recipient was 0.16 in the first 30 days. A similar incidence (0.17) was observed in the EXPAND Heart CAP study.

A total of 27 donor hearts in the EXPAND Heart, EXPAND Heart CAP, and PROCEED II studies were turned down for transplant following preservation using the OCS Heart System. Pathological signs of myocardial injury were observed in some of these turned-down donor hearts. It is unknown whether the injury was due to preservation with the OCS Heart System or predated preservation. Further investigations into the issue are warranted.

C. Benefit-Risk Determination

The probable benefits of preservation of donor hearts using the OCS Heart System include utilization of qualified donor hearts that otherwise would not have been utilized due to the limitations of the cold storage method.

The probable risks of preservation of donor hearts using the OCS Heart System include HGRSAEs, including graft failure.

Additional factors considered in determining probable risks and benefits for the OCS Heart System device included limitations of the single-arm design of the EXPAND Heart study, the lower overall survival trend in the OCS arm compared to the SOC arm in PROCEED II, and the persistent shortage of donor hearts in the U.S. As a result, the device should be used not as a substitute for, but as a supplement to the cold storage preservation method.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives.

In conclusion, given the available information above, the data support that for DBD hearts deemed unsuited for procurement and transplantation at initial evaluation due to limitations of prolonged cold static cardioplegic preservation (e.g., > 4 hours of cross-clamp time), the probable benefits of preservation using the OCS Heart System outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use, which limit the use of the device to scenarios where it is determined at initial evaluation that the DBD heart is unsuited for procurement and transplantation due to limitations of prolonged cold storage preservation method (e.g., > 4 hours of cross-clamp time).

XIV. CDRH DECISION

CDRH issued an approval order on September 3, 2021. The final clinical conditions of approval cited in the approval order are described below.

The applicant must conduct three post-approval studies:

1. ***Ex Vivo* Study on Myocardial Injury**: This study should be conducted per the protocol, entitled "OCS Heart Post-Approval Animal Protocol" (protocol number: OCSHEART-01-AnPAS), dated August 23, 2021. The objective of the study is to further investigate whether there is a correlation between donor heart preservation using the OCS Heart System and myocardial injury. The study will be a controlled study, with the control being standard cold static cardioplegic storage. All preserved hearts will undergo blinded histological examinations.

2. **Continued Follow-up of the Premarket Cohort**: This study should be conducted per the protocol, entitled "OCS Heart EXPAND + CAP Continued Follow-Up Post-Approval Study" (protocol number: OCS-HEART-02-PAS), dated August 23, 2021. The study will consist of all living patients who were enrolled under the IDE, including those enrolled under the Continued Access Protocol (CAP) investigation. The objective of the study is to characterize the clinical outcomes annually through 5 years post-transplant. The safety and effectiveness endpoints include patient survival, cardiac-related patient survival, and heart graft survival through 5 years post-transplant.

3. **Post-commercialization New Enrollment Study**: This study should be conducted per the protocol, entitled "OCS Heart Perfusion Post-Approval Registry Protocol" (protocol number: OCSHEART-01-ClinPAS), dated August 23, 2021. The study will enroll a total of 200 patients that constitute the Primary Analysis Population, or enroll for a period of 2 years, whichever is longer, at up to 40 U.S. heart transplant centers. The objective of the study is to characterize the performance of the OCS Heart System in the real-world setting, as compared to concurrent control data obtained from the United Network for Organ Sharing (UNOS) database for recipients of standard criteria donor hearts preserved using cold static cardioplegic storage. The primary endpoint of the study is patient survival at 1 year post-transplant. Other endpoints include patient/graft survival through 5 years post-transplant, incidence of moderate or severe primary graft dysfunction (PGD; left or right ventricle), and incidence of donor heart turndowns following OCS Heart System perfusion.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

Baran DA, Copeland H, and Copeland J. What Number Are We? Donor Sequence and Outcomes of Heart Transplantation. *Circulation: Heart Failure* 2019; 12(5):e005823.