DRAFT SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Ex Vivo Portable Organ Perfusion System for Donor Hearts
Device Trade Name:	OCS™ Heart System
Applicant's Name and Address:	TransMedics, Inc. 200 Minuteman Road, Suite 302 Andover, MA 01810
Premarket Approval Application (PMA) Number:	Pxxxxxx
Date(s) of Panel Recommendation:	April 6, 2021
Date of Good Manufacturing Practice Inspection:	N/A
Date of Notice of Approval to the Applicant:	TBD

II. INDICATIONS FOR USE

The TransMedics® Organ Care System (OCS™) Heart System is a portable extracorporeal heart perfusion and monitoring system indicated for the resuscitation, preservation, and assessment of donor hearts in a near-physiologic, normothermic and beating state intended for a potential transplant recipient. OCS Heart is indicated for donor hearts with one or more of the following characteristics:

- Expected cross-clamp or ischemic time ≥ 4 hours due to donor or recipient characteristics (e.g., donor-recipient geographical distance, expected recipient surgical time); or
- Expected cross-clamp or ischemic time ≥ 2 hours AND one or more of the following:
  - Donor Age ≥ 55 years; or
  - Donors with history of cardiac arrest and downtime ≥ 20 minutes; or
  - Donor history of alcoholism; or
  - Donor history of diabetes; or
  - Donor Left Ventricular Ejection Fraction (LVEF) ≤ 50% but ≥ 40%; or

- Donor history of Left Ventricular Hypertrophy (LVH) (septal or posterior wall thickness of > 12 ≤ 16 mm); or
- Donor angiogram with luminal irregularities but no significant coronary artery disease (CAD).

III. CONTRAINDICATIONS

Do not use the OCS Heart System if any of the following conditions exist.

- Moderate to severe aortic valve incompetence in donor heart
- Observed myocardial contusion on donor heart
- Known unrepaired interatrial or interventricular defects including patent foramen ovale.

IV. WARNINGS AND PRECAUTIONS

Refer to the labeling for applicable warnings and precautions.

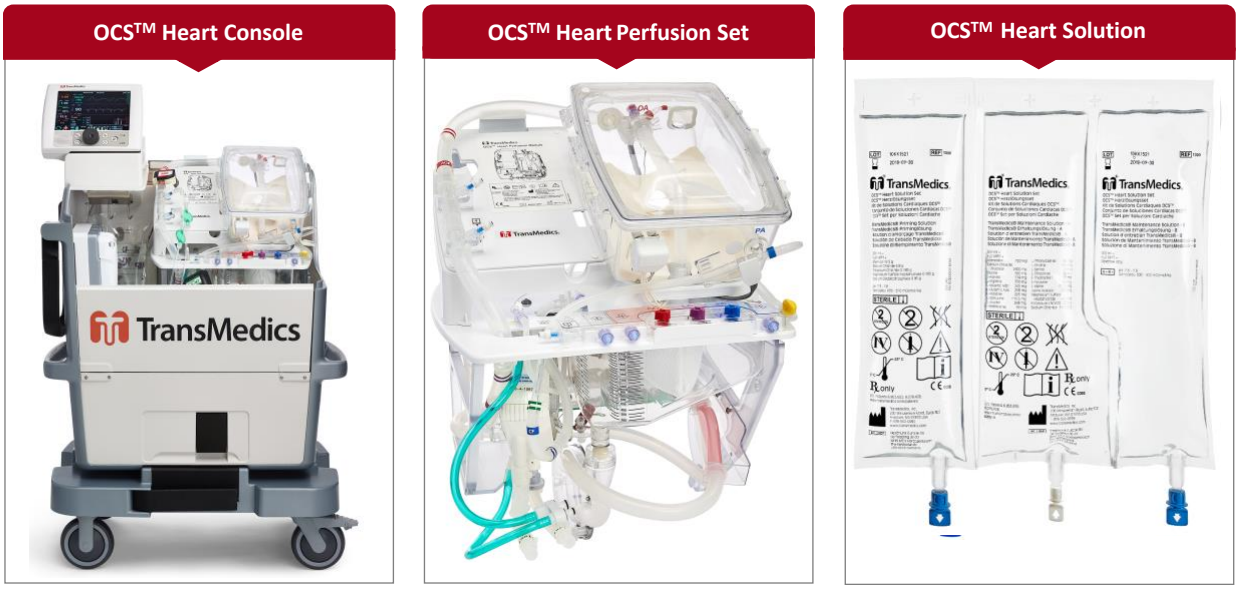
V. DEVICE DESCRIPTION

The OCS Heart System consists of:

- The OCS Heart Console (Heart Console)
- The OCS Heart Perfusion Set (HPS) – comprised of Heart Perfusion Module (HPM) and HPS Accessories
- The OCS Heart Solution Set – comprised of two heart preservation solutions, which are the OCS Priming Solution and the OCS Maintenance Solution.

These three major components are shown in Figure 1 below.

Figure 1: Components of the OCS Heart System



A. Description of Major Components

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 HPM and the disposable HPS Accessories. The HPM provides a closed circulatory system to protect, maintain, and support the 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 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.

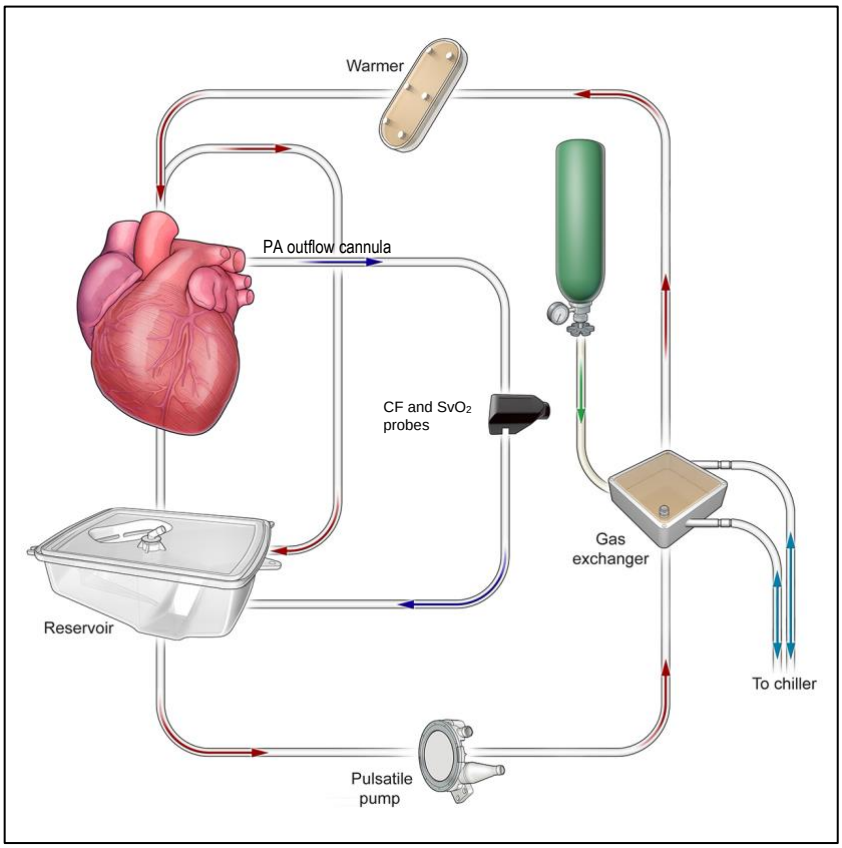
OCS Heart Solution Set: The OCS Heart Solution Set consists of two proprietary heart preservation solutions - the OCS Priming Solution and the OCS Maintenance Solution. Additives are required at the time of use that are supplied and added by the user.

The OCS Heart Solution Set is not intended to be administered directly to the donor or the recipient.

B. Mode of Action

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. The circuit is illustrated in Figure 2 below. 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 blood 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 Fluid Flow



To adequately perfuse the heart, the OCS Heart System controls and monitors the preservation environment. The user can adjust blood flow rate, solution delivery rate, gas flow rate, and blood temperature within specified ranges, all of which contribute to the ability to adequately perfuse the donor heart. The OCS 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

Conventional procedures used in the preservation of donor hearts are limited to cold, static storage of the donor heart in a hypothermic preservation solution prior to transplantation. Other options are not to receive a heart transplant, which would mean the patient would remain on the transplant waiting list, and may undergo circulatory/mechanical support, such as implantation of a ventricular assist device (VAD). In the U.S., 16% of the patients on the transplant waiting listing will either expire while waiting or become too ill to be transplanted.

There are no other legally marketed devices in the U.S. that provide portable *ex-vivo* perfusion and monitoring of donor hearts.

VII. MARKETING HISTORY

The OCS Heart System has been CE marked and approved for use in the EU since 2006. It is also approved for use in Australia, Saudi Arabia, United Arab Emirates, Israel, Taiwan, and Kazakhstan.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Heart transplant patients, regardless of the method of donor organ preservation, may experience any of the following adverse events.

- Acute rejection
- Airway anastomotic complications
- Arrhythmia
- Aspiration
- Bleeding (major)
- Death
- 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.

IX. SUMMARY OF NONCLINICAL STUDIES

TransMedics conducted the following nonclinical studies to evaluate the OCS Heart System: (A) engineering bench testing; (B) biocompatibility; (C) software verification and validation; (D) cybersecurity; (E) electrical and medical device safety; (F) electromagnetic compatibility; (G) wireless technology; (H) sterilization; (I) shelf life; and (J) animal functional testing.

A. Engineering Bench Testing

TransMedics performed engineering bench testing on the OCS Heart System, the Heart Console, and the HPS to demonstrate that the device meets its product requirements and specifications. In cases when testing was performed on an earlier version of the device, the later design changes did not affect the functions or specifications under evaluation.

B. Biocompatibility

TransMedics performed a series of biocompatibility studies to demonstrate the safety of the materials of the TransMedics HPS. All studies were conducted in compliance with 21 CFR Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies (GLPs).

The HPS has been categorized for its body contact and duration of contact according to ISO 10993-1, Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing, to select the appropriate biocompatibility testing program.

Biocompatibility tests and results are provided in Table 1 below.

Table 1: Summary of the Biocompatibility Testing

Biocompatibility Test	ISO Test Standard	Results
Cytotoxicity Test (MEM Elution)	10993-5	Non-cytotoxic
Pyrogenicity (USP <151> Rabbit Pyrogen)	10993-11	Non-pyrogenic
Hemocompatibility (2 methods, direct and indirect contact)	10993-4	Non-hemolytic
Sensitization (Guinea Pig Maximization, 2 extracts)	10993-10	No delayed dermal contact sensitization
Intracutaneous Reactivity (2 extracts)	10993-10	No irritation
Acute Systemic Toxicity (2 extracts)	10993-11	No systemic toxicity observed
Genotoxicity (3 methods, 2 extracts each) • *in vitro* Bacterial Reverse Mutation • *in vitro* Mouse Lymphoma Assay • *in vivo* Mouse Peripheral Blood Micronucleus Assay	10993-3	Non-mutagenic
USP Physicochemical Tests: • Non-volatile residue • Residue on Ignition • Heavy Metals • Buffering Capacity	USP<661> Containers, Plastics	Meets USP limits; no significant extractables

All materials used to manufacture the OCS Heart Solution Set meet compendial requirements; thus, they are suitable and safe for their intended use. The results from analyses of the finished product included pH, osmolality, color, clarity, chemical analysis, particle size, sterility, and endotoxins. The tests performed on the finished product were all within specification. This Process Verification demonstrated that the OCS Heart Solution Set consistently fulfills the qualification requirements and meets specifications.

C. Software Verification and Validation

TransMedics performed system level software verification and validation testing to demonstrate the OCS Heart System performs as intended. 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." Verification and validation testing included unit tests, static analysis, system level verification tests (which included functional testing to demonstrate the device met its requirements), code review, and validation testing.

D. Cybersecurity

The OCS does not contain the hardware or software required for many common network interfaces such as USB, Ethernet, or Wi-Fi. The OCS Heart System incorporates a Wireless Monitor dedicated to the Heart Console. The Wireless Monitor communications with the OCS Console using one of two redundant communication interfaces - hard-wired or Bluetooth. A cybersecurity incident affecting an OCS could not directly result in harm to multiple organs because the OCS is not connected to any other device, network or the internet. Accordingly, because the OCS does not connect to a network, the internet or another medical device/product coupled with the fact that a cybersecurity incident cannot result in harm to multiple organs, it is considered Tier 2 (Standard Cybersecurity Risk).

To address potential cybersecurity risks, TransMedics provided information according to FDA guidance entitled, "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices." This information included, among other things, 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 TransMedics has appropriate controls in place to identify, protect, detect, respond, and recover from cybersecurity threats per the FDA guidance.

E. Electrical and Medical Device Safety

The OCS Heart System was tested to demonstrate that it meets the requirements for medical device safety, including electrical safety. The system was tested by an outside laboratory according to the Edition 3.1 of the IEC 60601-1 standard, as well as the ANSI/AMMI and CSA versions of the standard. The results are shown in Table 2 below.

Table 2: Summary of Electrical, Thermal, and Mechanical Safety Testing

Test Description	IEC/ANSI/AAMI 60601-1: 2005 +A1:2012 Clause	Result
General Requirements	4	Pass
General Requirements for Testing ME Equipment	5	Pass
Classification of ME Equipment and ME Systems	6	Pass
ME Equipment, Identification Marking and Documents	7	Pass
Protection Against Electrical Hazards from ME Equipment	8	Pass
Protection Against Mechanical Hazards of ME Equipment and ME Systems	9	Pass
Protection Against Unwanted and Excessive Radiation Hazards	10	Pass
Protection Against Excessive Temperatures and Other Hazards	11	Pass

Test Description	IEC/ANSI/AAMI 60601-1: 2005 +A1:2012 Clause	Result
Accuracy of Controls and Instruments and Protection Against Hazardous Outputs	12	Pass
Hazardous Situations and Fault Conditions	13	Pass
Programmable Electrical Medical Systems (PEMS)	14	Pass
Construction of ME Equipment	15	Pass
ME Systems	16	Pass

F. Electromagnetic Compatibility (EMC)

The OCS Heart System was tested to demonstrate that it meets the requirements for radio frequency emissions and radio frequency susceptibility (together, EMC). The system was tested by an outside laboratory according to standards for EMC requirements of electrical equipment (IEC 60601-1-2 (4th edition) – Group 1, Class A, non-life supporting equipment, CISPR 25, and RTCA DO-160G). The OCS Heart System met the requirements of the standards. The results are shown in Table 3 below.

Table 3: Summary of Emission and Immunity Testing

Test	Standard	Results
Radiated Emissions	EN55011/FCC Part 15 (CISPR 11)	Pass
AC Mains Conducted Emissions	EN55011/FCC Part 15 (CISPR 11)	Pass
Harmonics Emissions	IEC 61000-3-2	Pass
Voltage Fluctuation/ Flicker	IEC 61000-3-3	Pass
Electrostatic Discharge Immunity	IEC 61000-4-2	Pass
Immunity to proximity fields from RF wireless communications equipment	IEC 60601-1-2 Clause 8.10	Pass
Radiated RF Immunity	IEC 61000-4-3	Pass
Electrical Fast Transients Immunity	IEC 61000-4-4	Pass
Surge Immunity	IEC 61000-4-5	Pass
Conducted RF Immunity	IEC 61000-4-6	Pass
Magnetic Field Immunity	IEC 61000-4-8	Pass
Voltage Dips/Interrupts	IEC 61000-4-11	Pass
Radiated Immunity	ISO 7137 and RTCA DO 160G	Pass
Radiated Emissions	ISO 7137 and RTCA DO 160G	Pass
Radiated Emissions	CISPR 25	Pass
Spurious Emissions	FCC 47 CFR Part 15C	Pass

G. Wireless Technology

The wireless connection between the OCS Console and Wireless Monitor is a peer-to-peer Bluetooth connection. TransMedics addressed the recommendations presented in the FDA guidance entitled, "Radio Frequency Wireless Technology in Medical Devices," and performed successful wireless coexistence testing according to the IEEE article, "An Experimental Method for Evaluating Wireless Coexistence of a Bluetooth Medical Device."

H. 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, Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals.

The OCS Heart Solution Set is steam sterilized. The sterilization cycle was validated to achieve a minimum SAL of 10^{-6} according to European Pharmacopoeia 5th edition 5.0 General Texts Chapter 5.1 page 445 – 450; General texts on Sterility and U.S. Pharmacopeia USP 28 NF 23 General Information Chapter <1211>; Sterilization and Sterility Assurance.

I. Shelf Life Testing

Package integrity and simulated shipping testing was performed for the HPS and OCS Heart Solution Set to confirm that package integrity can be maintained during shipping. Real-time and accelerated shelf life testing demonstrates the safety and suitability of the HPS for the labeled shelf life.

In addition, real-time and accelerated shelf life testing supports the safety and suitability of the OCS Heart Solution Set for the labeled shelf life.

J. Animal Functional Testing

TransMedics performed multiple functional animal studies to evaluate the safety, suitability, and effectiveness of the OCS Heart System for the preservation of donor hearts.

The animal studies used a porcine model to evaluate the performance of the OCS Heart System because it is a large animal model frequently used for thoracic work. The anatomy and size of the pig's heart closely resembles the human heart, making it a clinically suitable animal model that is feasible and practical to use in the laboratory setting.

The testing demonstrated that the OCS Heart System adequately maintained and perfused the donor heart on the OCS when used in accordance with the current use model. 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. All acceptance criteria were met.

The data validated the ability of the OCS Heart System to meet the performance specifications and that the configuration of the OCS Heart System worked successfully during simulated surgical procedures.

X. SUMMARY OF CLINICAL STUIDES

The primary clinical data set supporting this PMA application is the OCS Heart EXPAND trial and the OCS Heart EXPAND Continued Access Protocol (CAP). Additional data included in this PMA are the results of the PROCEED II trial and published long-term international studies of the OCS Heart System for standard criteria, extended criteria and DCD hearts.

A. OCS Heart EXPAND Trial

The primary clinical data sets supporting FDA approval of the OCS Heart System are the OCS Heart EXPAND trial and the OCS Heart EXPAND CAP. The following sections describe the OCS Heart EXPAND trial and results, followed by the pooled analysis of the OCS Heart EXPAND trial and the OCS Heart EXPAND CAP trials.

The purpose of the OCS Heart EXPAND trial was to evaluate the effectiveness of the OCS Heart System to resuscitate, preserve and assess donor hearts that may not meet current standard donor heart acceptance criteria for transplantation. In addition to assessing the impact of the OCS Heart System on expanding donor heart utilization from extended criteria donors, given that the OCS Heart EXPAND was the first of its kind trial, it also provided important short and long term clinical outcome data for these types of donor heart transplants in a prospective fashion.

1. Study Design

OCS Heart EXPAND trial was a prospective, single arm, multi-center trial of 75 transplanted subjects at 9 U.S. investigational sites.

a) Primary Effectiveness Endpoint

The primary effectiveness endpoint is a composite of patient survival at Day 30 post-transplant and freedom from severe ISHLT Primary Graft Dysfunction (PGD) at 24 hours post-transplant (as defined in Appendix 2 of the protocol according to ISHLT consensus manuscript (Kobashigawa, et al., 2014)). The primary hypothesis for the trial was that the true proportion of transplanted recipients with the composite of patient survival at Day 30 post-transplantation and freedom from severe PGD in the first 24 hours post-transplantation was greater than the performance goal value of 0.65 (65%). Given the lack of published literature on post-transplant clinical outcomes from these types of donor hearts at the time the OCS Heart EXPAND trial was being designed, the sponsor established this OPG based on published literature for standard criteria heart transplantation incidence of severe PGD of ~30% and on published OPTN/SRTR reports of 30-day patient mortality of ~5%.

b) Secondary Effectiveness Endpoints

- Patient survival at Day-30 post-transplantation.
- Incidence of severe ISHLT primary heart graft dysfunction (PGD) (left or right ventricle) in the first 24 hours post-transplantation (as defined in Appendix 2 of the protocol according to ISHLT consensus manuscript).
- Rate of donor heart utilization (i.e., the percentage of donor hearts successfully transplanted after preservation and assessment on the OCS Heart System).

c) Additional Clinically Relevant Analyses

Additional analyses include:

- Patient survival at Day 30 and hospital discharge if longer than 30 days
- Patient survival at 6- and 12-months post-transplant.

d) Safety Endpoint

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), as defined in Appendix 2 of the protocol according to ISHLT consensus manuscript (Kobashigawa, et al., 2014)
- Primary graft failure requiring re-transplantation.

2. Trial Population

Patients were heart transplant recipients and donors who met inclusion and exclusion criteria.

a) Inclusion Criteria

Donor: At least one of the following:

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

Recipient - Day of Transplant:

- Registered male or female primary heart transplant candidate and
- Age ≥ 18 years old and

- Signed: (1) written informed consent document and (2) authorization to use and disclose protected health information.

b) Exclusion Criteria

Donor:

- 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.

3. Donor Heart on OCS Acceptance Criteria

All donor hearts preserved on the OCS Heart System should meet the following clinical criteria for transplantation at final assessment on the OCS Heart System:

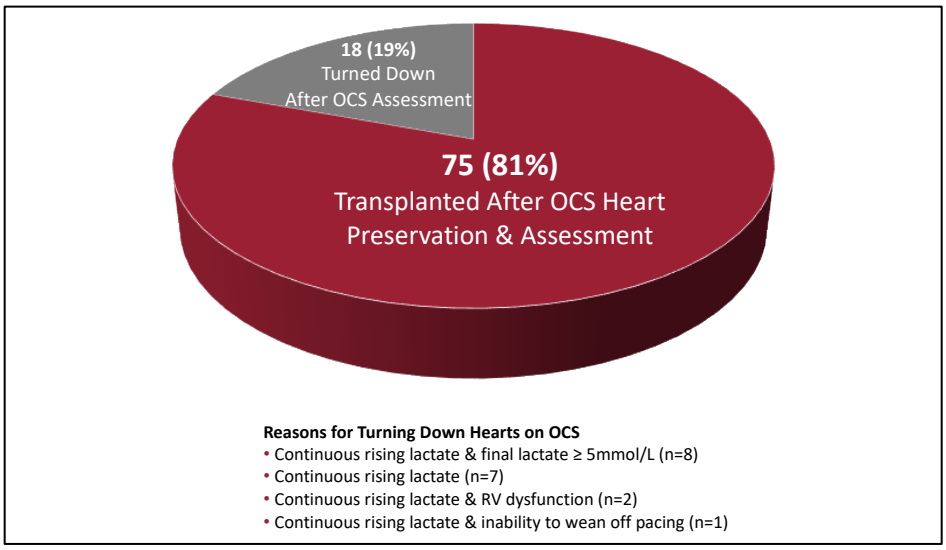
- Final total arterial circulating perfusate lactate level < 5 mmol/L with stable lactate trend.
- Stable CF, AOP trends within ranges after stabilization (certain expanded criteria organs, e.g., LVH hearts, may require higher CF and/or AOP to achieve adequate perfusion)
  - Aortic Pressure (mean AOP): 40-100 mmHg
  - Coronary Flow (CF): 400-900 ml/min.

In addition, to clinical judgment of the transplanting surgeon, arterial lactate trend on OCS was used to determine acceptance criteria of donor hearts perfused on OCS. Arterial lactate has been shown to be a sensitive marker for adequacy of OCS perfusion of the donor heart and post-transplant outcomes following OCS perfusion.

4. Donor Heart Disposition

In the OCS Heart EXPAND trial, a total of 93 donor hearts were preserved and assessed on OCS and of these, 75 were transplanted, giving a utilization rate of 81% (see Figure 3).

Figure 3: OCS Heart EXPAND Trial Donor Utilization



This is a clinically important result, given that donor hearts were rejected by other centers and likely would not have been utilized outside of the OCS Heart EXPAND trial. Table 4 below shows the donor match run data available from UNOS for the 93 donor hearts preserved on the OCS Heart System for the OCS Heart EXPAND trial. These 93 hearts were refused for transplant by other centers an average of 66 times (median 29) before acceptance into the OCS Heart EXPAND trial. For reference, from 2007-2014, the median number of refusals for heart transplants in the U.S. was 2 (Baran, et al. 2019), which further suggests that the donor hearts transplanted in the OCS Heart EXPAND trial would likely have gone unutilized outside of the trial.

Table 4: Donor Heart Offers Refusals Prior to Acceptance in OCS Heart EXPAND Trial

	Donor Heart Offers from UNOS Donor Match Run Data (N = 93)
Mean number of Refusals per donor heart (Mean ± SD)	66 ± 90
Median number of Refusals per donor heart	29
Minimum - Maximum	0 - 379

5. OCS Heart EXPAND Trial Recipients Enrollment

There were 96 patients who signed informed consent with data in the database. Of these, 6 patients were not matched with a donor heart that was instrumented on the OCS: 4 of the subjects were matched with a standard criteria donor heart, 1 patient became ineligible (delisted for transplant), and 1 patient was withdrawn and transplanted with a donor heart preserved on ice due to logistics.

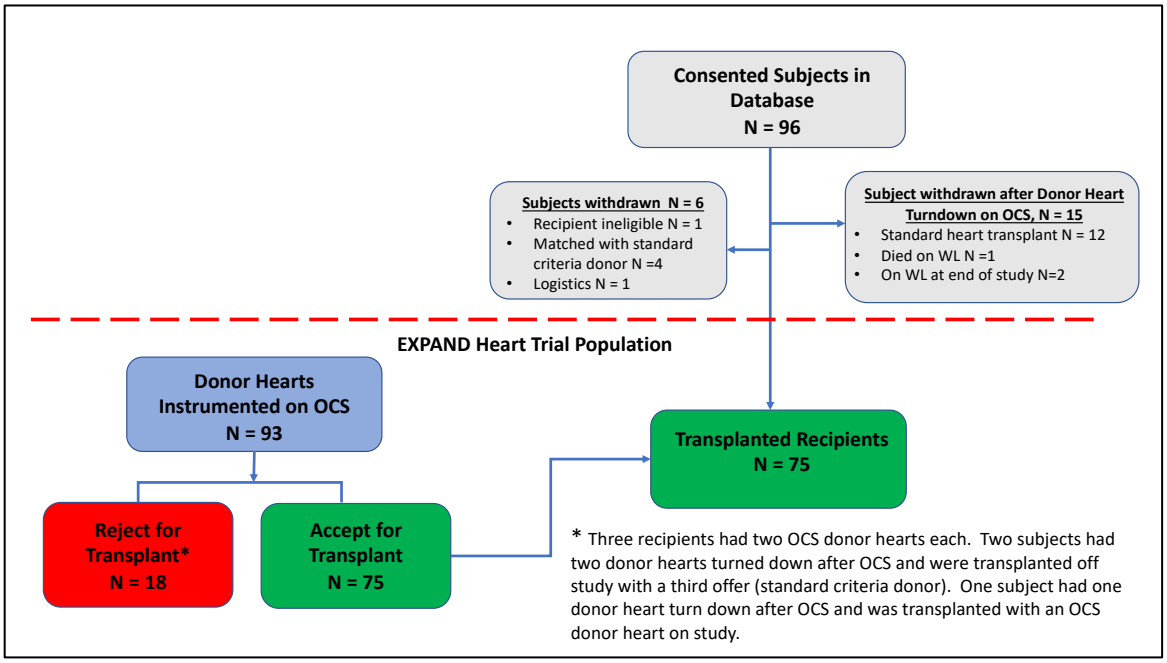
Sixteen (16) patients experienced donor heart turndown following OCS preservation. The disposition of these 16 patients was as follows:

- 10 patients were transplanted outside of the study with a subsequent standard criteria donor offer preserved on cold storage after one OCS turndown.

- 2 patients were transplanted outside of the study with a subsequent standard criteria donor offer preserved on cold storage after two OCS turndowns.
- 3 patients remained on the waiting list after OCS turndown. Two of these patients were alive and one patient had died by the end of the study.
- 1 patient was transplanted in the OCS Heart EXPAND trial with a second donor offer preserved on OCS after one OCS turndown.

Therefore, the transplanted recipient population consists of 75 subjects who were transplanted with donor hearts preserved on the OCS Heart System. The analyses of all effectiveness and safety endpoints were based on the transplanted recipient population. The OCS Heart EXPAND transplanted recipient population is illustrated in Figure 4 below.

Figure 4: OCS EXPAND Heart Trial Population



6. Recipients Demographic Characteristics and Risk Factors

The recipient demographics are shown in Table 5 below. The majority of recipients (69%) were status 1A and were on mechanical circulatory support at the time of transplant (64%). Recipient characteristics are also presented by known risk factors for heart transplant recipients (Sorabella, et al., 2015; Trivedi, et al., 2016).

Table 5: Recipient Demographics in OCS Heart EXPAND Trial

Recipient Characteristics	OCS Transplanted Recipients N=75
Age (years) mean ± SD	55.5 ± 12.6
Age > 65	18 (24.0%)
Gender – male n (%)	61 (81.3 %)
BMI (kg/m^2) – mean ± SD	27.7 ± 4.7

Recipient Characteristics	OCS Transplanted Recipients N=75
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%)
• LVAD	47 (62.7%)
• RVAD	0 (0%)
• BiVAD	1 (1.3%)
• ECMO	0 (0%)
Status n (%):	
• 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%)
Female donor to male recipient mismatch	12 (16.0%)
Renal dysfunction	11 (14.7%)
PRA (%) mean (range)	7.9 (0-81)

7. Donor Demographic Characteristics and Risk Factors

This trial enrolled a very complex group of donor hearts with many exhibiting multiple inclusion criteria. To illustrate this complex nature of the multiple criteria donor hearts enrolled in the OCS Heart EXPAND trial, Figure 5 below shows the detailed inclusion criteria for all 93 donor hearts that were enrolled and assessed on the OCS Heart System.

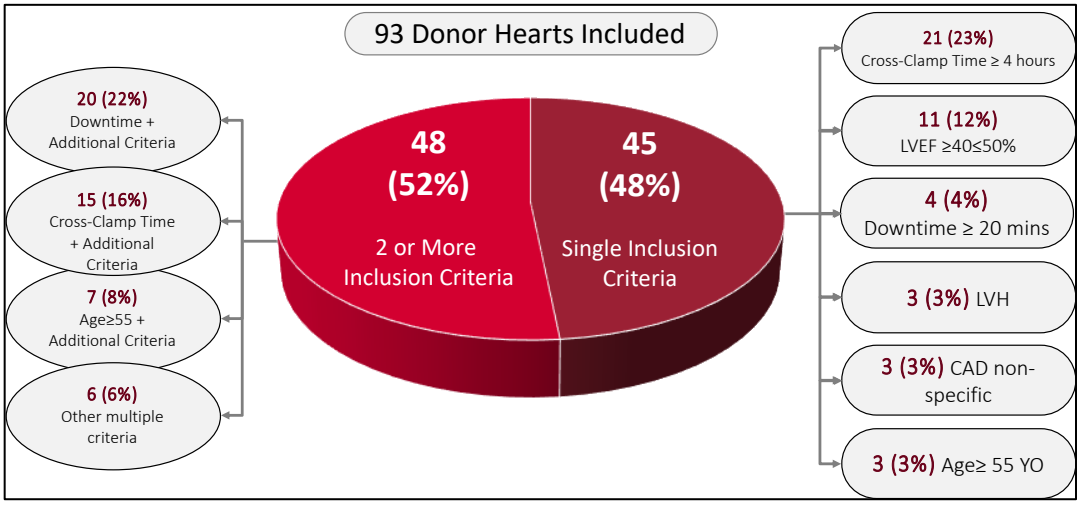
This complex donor criteria were also reflected in the donors that were transplanted in the OCS Heart EXPAND trial inclusion criteria (Table 6). Thirty-five (35) of the 75 transplanted donor hearts (47%) met more than one inclusion criterion.

Table 6: Donor Inclusion Criteria Met for Transplanted Hearts in the OCS Heart EXPAND Trial

Parameter	OCS Transplanted Donors N=75
Donor Inclusion Criteria Met n (%)*	
Expected Cross-Clamp Time ≥ 4hr	28 (37.3%)
Donor Age ≥ 55	10 (13.3%)
LVH	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 cath data	1 (1.3%)
Donors with Multiple Criteria	35/75 (46.7%)

*Donor inclusion criteria presented reflect additional review and verification of source documentation by TransMedics during PMA review.

Figure 5: Donor Hearts in OCS EXPAND Trial Meeting One, Two, or More Inclusion Criteria*



* Donor inclusion criteria presented reflect additional review and verification of source documentation by TransMedics during PMA review.

8. Comparison of Donor characteristics and Risk factors: OCS Heart EXPAND vs UNOS/SRTR Standard Criteria Donor Hearts

An analysis was performed to compare the OCS Heart EXPAND donor hearts to the donor hearts recorded in the UNOS/SRTR national database to establish that the OCS Heart EXPAND donor hearts were seldom utilized for transplant in the US today. The analysis was performed with de-identified data from the UNOS/SRTR database, which included all heart transplant recipients in the U.S. from January 2015 through December 2018 (i.e., the years that Heart EXPAND was conducted).

The UNOS/SRTR cohort includes 10,426 adult heart transplants, and it excluded any transplants in the OCS Heart EXPAND trial. It is important to note that the analysis could only evaluate donor risk factors that are collected in the UNOS/SRTR database. Some of the OCS Heart EXPAND donor characteristics/risk factors are not captured in the UNOS/SRTR database, such as LVH and coronary artery luminal irregularities, since they are historically considered to be major risk factors for heart donation and these hearts are seldomly used for transplantation. Therefore, the analysis assessed the available donor characteristics/risk factors for the N=10,426 donor hearts in the UNOS/SRTR cohort and compared them to the same risk factors in the N=93 donor hearts in the OCS Heart EXPAND trial (see Table 7 below).

The data demonstrate that the EXPAND donors are not routinely transplanted on cold storage in the U.S. today. This is further demonstrated when considering donors transplanted in the U.S. on cold storage with two or more donor inclusion criteria (which comprised 52% of the donor hearts in the OCS Heart EXPAND trial). As shown in Table 7 below, of the 10,426 donor hearts preserved on cold storage in 2015-2018:

- Only 5% of donor hearts had cross-clamp time ≥ 4 hrs and one other criterion (e.g., either downtime ≥ 20 min or alcoholism or diabetes or LVEF 40-50%)
- Only 1% of donor hearts had donor age ≥ 55 and one other criterion (e.g., either downtime ≥20 min or alcoholism or diabetes or LVEF 40-50%)
- Only 0.6% of donor hearts had downtime ≥ 20 minutes and one other criterion (e.g., either alcoholism, diabetes or LVEF 40-50%).

These data, in conjunction with the UNOS donor match run data described in Table 4, show that the donor hearts preserved on OCS in the OCS Heart EXPAND trial are not routinely transplanted today, and this is an important clinical consideration in the assessment of the benefits and risks of the OCS Heart System to increase the number of successful heart transplants in the U.S.

Table 7: Donor Characteristics for EXPAND vs. UNOS/SRTR Hearts transplanted 2015-2018

Donor Characteristics	Expand OCS (N=93)	SRTR (N=10,426)	p-value
Age (yr) – Mean ± SD	36.3 ± 13.1	32.0 ± 11.0	0.0022
Age ≥ 55 - n (%)	11 (11.8%)	295 (2.8%)	<0.0001
LV Ejection Fraction % - Mean ± SD	57.4 ± 8.7	61.7 ± 6.5	<0.0001
Cross-Clamp Time ≥ 4 Hours – n (%) (Expected)	37 (39.8%)	1607 (15.4%)	<0.0001
Cross-Clamp Time ≥ 4 Hours – n (%) (Actual)	72 (96.0%)	1607 (15.4%)	<0.0001

Donor Characteristics	Expand OCS (N=93)	SRTR (N=10,426)	p-value
LVEF between 40% - 50% - n (%)	24 (25.8%)	481 (4.6%)	<0.0001
Down Time ≥ 20 Minutes – n (%)	33 (35.5%)	240 (2.3%)	<0.0001
Social History of Alcoholism – n (%)	10 (10.8%)	1756 (16.8%)	0.1266
History of Diabetes - n (%)	3 (3.2%)	383 (3.7%)	1.0000
a. Cross-Clamp Time ≥ 4 h and (Age (yr) ≥ 55 or Downtime ≥ 20 Min. or History of Alcoholism or History of Diabetes or LVEF 40-50%) – n (%)	13 (14.0%)	464 (4.5%)	0.0003
b. Age (yr) ≥ 55 and (Downtime ≥ 20 Min. or History of Alcoholism or History of Diabetes or LVEF 40-50%) – n (%)	7 (7.5%)	104 (1.0%)	<0.0001
c. Downtime ≥ 20 Min. and (History of Alcoholism or History of Diabetes or LVEF 40-50%) – n (%)	9 (9.7%)	58 (0.6%)	<0.0001

9. Donor Heart Preservation Characteristics and Critical Times

Donor heart preservation characteristics are shown in Table 8 below. Note that total cross-clamp time (total out-of-body time) is the time from aortic cross-clamp application in the donor to the pulmonary artery (PA) cross-clamp removal in the recipient, while the total ischemic time is the time that donor hearts were ischemic without any oxygenated perfusion.

Despite the total cross-clamp time that averaged over 6 hours (380.7 minutes), the OCS Heart System significantly reduced the injurious ischemic time for the hearts to less than 2 hours (102.1 minutes). These results are clinically significant since they support the potential of the OCS Heart System to facilitate long distance procurement to maximize donor heart utilization for transplantation while minimizing the negative impact of ischemic time for the donor hearts.

Table 8: Donor Heart Preservation Characteristics

Parameter	OCS Heart EXPAND (N=75)
Cross-clamp Time (mins)[1]	N=75
Mean ± SD	380.7 ± 93.2
Median	369.0
Min.- Max.	173 - 682
Total Ischemic Time (mins)[2]	N= 75
Mean ± SD	102.1 ± 22.6
Median	98.0
Min.- Max.	65 - 168
OCS Perfusion Time (mins)	N = 75
Mean ± SD	278.6 ± 83.3

Parameter	OCS Heart EXPAND (N=75)
Median	276.0
Min.- Max.	100 - 532

[1] Cross-clamp time is the time from aortic cross-clamp application time in the donor to the PA cross-clamp removal time in the recipient (Out of body time).

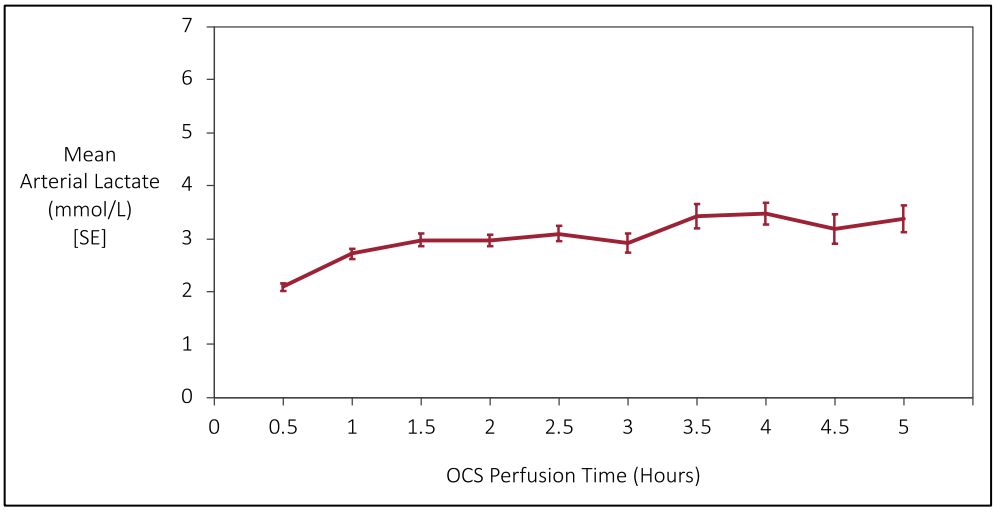
[2] Total ischemic time for hearts preserved by OCS is the cross-clamp time minus OCS perfusion time.

10. OCS Heart System Perfusion Parameters

The OCS Heart System perfusion parameters are summarized in Table 9 below. The donor hearts were maintained within the recommended parameters on the OCS Heart System.

Donor arterial baseline lactate level is a function of many different aspects of the donor demographics and retrieval environment and the lactate level in the donor is not optimized or controlled. Once the organ is placed on the OCS Heart System, the user has the ability to adjust the AOP and/or coronary flow to adequately perfuse the donor heart, resulting in a stable lactate profile. Further adjustments may then be made to maintain the lactate at acceptable levels. Figure 6 below demonstrates the average lactate trend for all donor hearts on the OCS Heart System that were accepted for transplantation in the OCS Heart EXPAND Trial.

Figure 6: Mean Lactate Levels During OCS Heart Perfusion for Donor Hearts Transplanted in EXPAND Trial



It is important to recognize that lactate trend was only considered as a clinical indicator for adequacy of perfusion, after adjustment and optimization of OCS Heart perfusion parameters and hemodynamics. The stability of perfusion parameters, heart hemodynamics as well as clinical judgement of heart contractility/rhythm on OCS also play key roles in deciding whether to accept or reject a donor heart on the OCS Heart System. Importantly, for many experienced OCS Heart clinical users, unstable and rising lactate trend despite multiple attempts to stabilize the perfusion parameters (CF and AOP) is a sign of compromised clinical condition of the donor heart which would lead them to turn down the heart for transplantation.

Table 9: OCS Heart System Perfusion Parameters

Parameter	OCS (N=75)
AOP Mean (mmHg)	N = 75
Mean ± SD	81.2 ± 7.8
Median	81.4
Min.- Max.	48 - 102
Coronary Flow (CF) (L/min)	n=75
Mean ± SD	0.74 ± 0.13
Median	0.756
Min.- Max.	0.05 - 0.93
Arterial Lactate (mmol/L) – Initial OCS Instrumentation	N = 75
Mean ± SD	1.9 ± 0.63
Median	1.750
Min.- Max.	0.93 - 3.80
Arterial Lactate (mmol/L) – Final OCS Instrumentation	N = 75
Mean ± SD	3.08 ± 0.95
Median	3.01
Min.- Max.	0.55 - 4.97
Pump Flow (L/min)	N= 75
Mean ± SD	1.13 ± 0.12
Median	1.12
Min.- Max.	0.93 - 1.76
Heart Rate (BPM)	N= 75
Mean ± SD	78.8 ± 2.5
Median	78.6
Min.- Max.	74 - 87
Hematocrit (%)	N = 74
Mean ± SD	21.1 ± 3.6
Median	20.7
Min.- Max.	16 – 33.0

11. Primary Composite Effectiveness Endpoint

Table 10 and Figure 7 below show the results of the composite primary effectiveness endpoint. The primary effectiveness endpoint met the pre-specified objective performance goal of 65% (p

<0.0001), and the results demonstrate that these extended criteria hearts, those seldom used for transplant today, can be transplanted successfully with favorable post-transplant outcomes.

Figure 7: Primary Composite Endpoint Results for the OCS Heart EXPAND Trial: Survival at 30 Days Post-transplant and Absence of ISHLT Severe PGD (LV or RV) Post-transplant

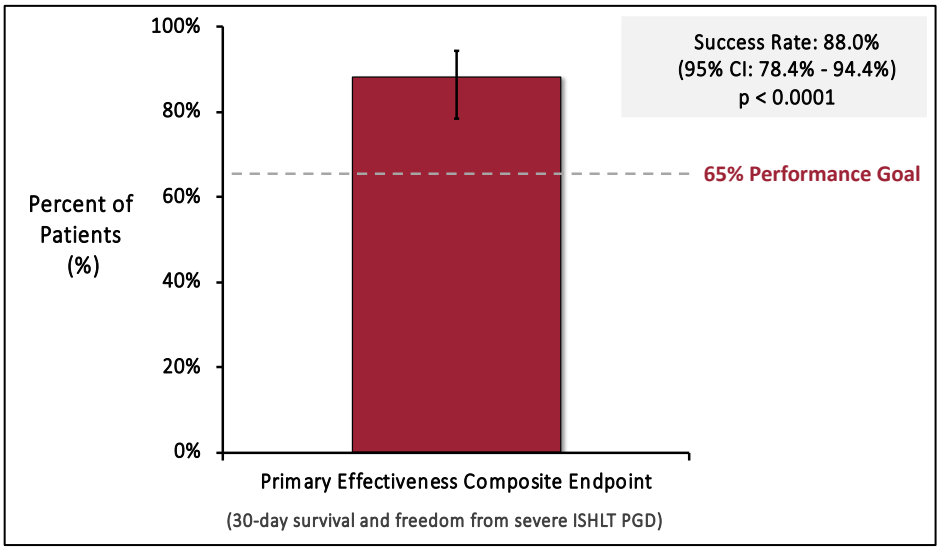


Table 10: Primary Effectiveness Endpoint for OCS Heart EXPAND Trial

Results for Primary Endpoint Composite and Components	OCS (N= 75)
Patient survival at day 30 post-transplantation and absence of severe PGD (left or right ventricle) in the first 24 hours post-transplantation	
Proportion (π[1]) (%) (n/N)	88.0% (66/75)
95% CI (%) for Proportion[2]	(78.4%, 94.4%)
p-value[3]	<0.0001

[1] π = n/N *100% = simple proportion.

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

[3] p-value from a one-sided exact binomial test, testing the null hypothesis that the true proportion is less than or equal to 0.65 versus the alternative hypothesis that it is greater than 0.65.

12. Secondary Effectiveness Endpoints

The secondary endpoints were the components of the composite primary endpoint. The results for the secondary endpoints are shown in Table 11 below and are discussed in more detail in the sections that follow.

Table 11: Secondary Endpoint Results for OCS Heart EXPAND Trial

Results for Secondary Endpoints (components of primary composite endpoint)	OCS (N= 75)
Patient survival at day 30 post-transplantation	

Results for Secondary Endpoints (components of primary composite endpoint)	OCS (N= 75)
Proportion (π[1]) (%) (n/N)	94.6% (70/74[3])
95% CI (%) for Proportion[2]	(86.9%, 98.5%)
Incidence of severe PGD (left or right ventricle) in the first 24 hours post-transplantation	
Proportion (π[1]) (%) (n/N)	10.7% (8/75)
95% CI (%) for Proportion[2]	(4.7%, 19.9%)

[1] π = n/N *100% = simple proportion.

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

[3] Excludes one subject with graft failure and re-transplant during the first 30 days

a) Patient Survival at 30 Days Post-Transplant

Patient survival at 30 days for OCS Heart EXPAND subjects was 94.6%. This result is comparable to the UNOS national average for 30-day survival following standard criteria donor heart transplantation, which is 95.7%.

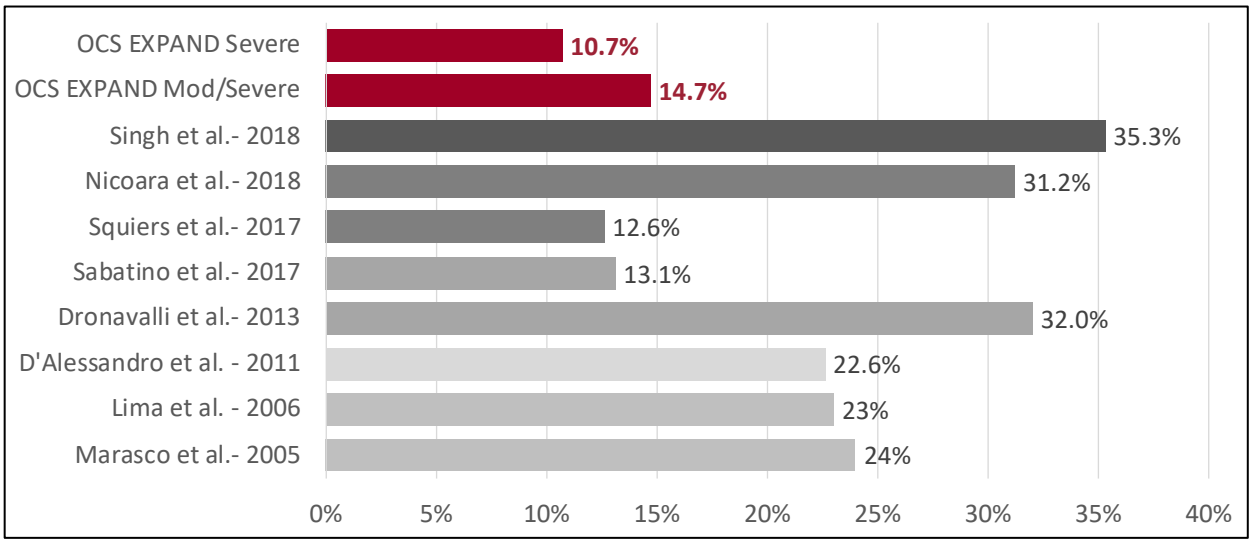
b) Incidence of Severe PGD (LV or RV) in the First 24 Hours Post-transplantation

The OCS Heart EXPAND protocol utilized the ISHLT consensus statement definition for severe PGD and the results were adjudicated by an independent medical monitor. The medical monitor utilized the ISHLT definition of PGD and the protocol definitions for the primary endpoint in his adjudications.

The incidence of severe ISHLT PGD in the first 24 hours post-transplantation was 10.7% and the incidence of moderate or severe PGD was 14.7%. (Moderate or severe PGD was a component of the primary safety endpoint, discussed in more detail in the sections that follow.)

These results were comparable to, or in some cases, lower than the values reported in the literature (Figure 8).

Figure 8: Comparison of PGD Rates for OCS Heart EXPAND Trial and Published Literature



13. Primary Safety Endpoint

The primary safety endpoint for the OCS Heart EXPAND trial was the number of heart graft-related serious adverse events (HGRSAEs) up to 30 days post-transplant, consisting of the following adverse events (at most one per type) if they are serious adverse events:

- Moderate or severe PGD (left or right ventricle) (not including rejection or cardiac tamponade) as defined by the ISHLT consensus definition
- Primary graft failure requiring re-transplantation.

All incidences of PGD were adjudicated by the Medical Monitor to determine whether the pre-specified ISHLT consensus definition was met.

The incidence on moderate or severe PGD (LV or RV) was 14.7%, and one patient had primary graft failure requiring re-transplantation. The mean number of HGRSAEs per patient was 0.2 ± 0.37 (Table 12).

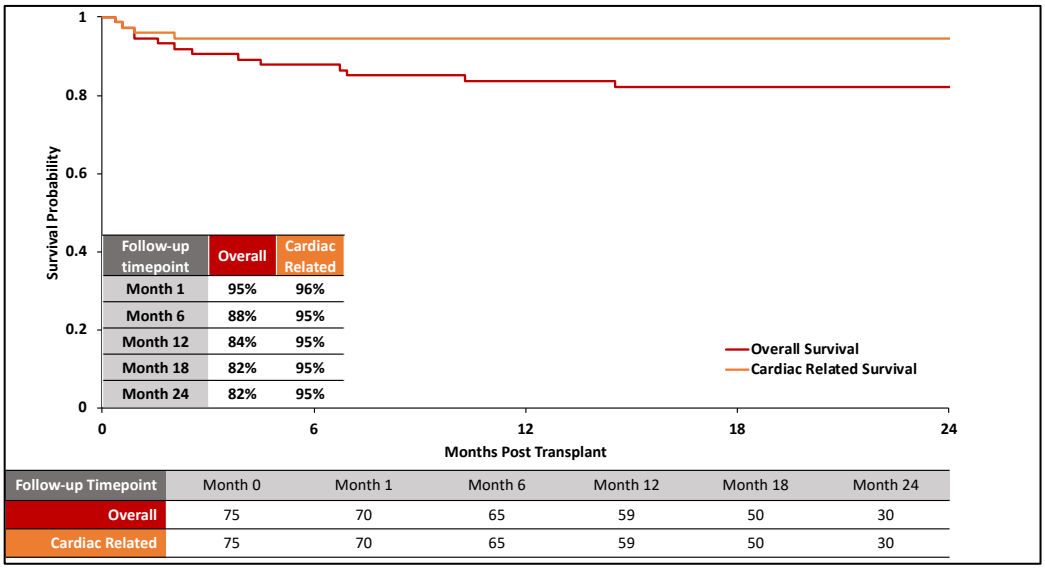
Table 12: Primary Safety Endpoint for OCS Heart EXPAND Trial and Listing of HGRSAEs

Primary Safety Endpoint and listing of HGRSAEs by type	**OCS Heart EXPAND N = 75**
Primary Safety Endpoint	
Mean ± SD	0.2 ± 0.37
Median	0.0
95% CI for Mean[1]	(0.1, 0.2)
HGRSAEs by Type	
Moderate or severe PGD (LV or RV), n/N (%)	11/75 (14.7%)
Primary Graft Failure requiring re-transplantation	1/75 (1.3%)
[1]Confidence interval calculated based on the t-distribution.	

14. Patient Survival

All transplanted recipients in the OCS Heart EXPAND trial have been followed through 12 months in the trial. In addition, survival data for the OCS Heart EXPAND subjects were obtained from the UNOS national database, giving follow-up beyond 12 months for subjects who had data entered in the database. The Kaplan-Meier Analysis of overall survival for OCS Heart EXPAND subjects is shown in Figure 9 below. Importantly, when considering the safety and effectiveness of the OCS Heart System as a heart preservation and assessment technology, it is clinically relevant to assess the number of cardiac-related deaths. There were 4 of a total of 13 deaths in the OCS Heart EXPAND trial through 14 months that were cardiac-related. Post-hoc Kaplan-Meier analysis of survival from cardiac-related death is also shown in Figure 9 below. Twelve-month freedom from cardiac-related death was 95% in the OCS Heart EXPAND trial.

Figure 9: Kaplan-Meier Analysis of Overall Survival and Cardiac-related Survival for OCS Heart EXPAND Subjects



Follow-up timepoint	Overall	Cardiac Related
Month 1	95%	96%
Month 6	88%	95%
Month 12	84%	95%
Month 18	82%	95%
Month 24	82%	95%

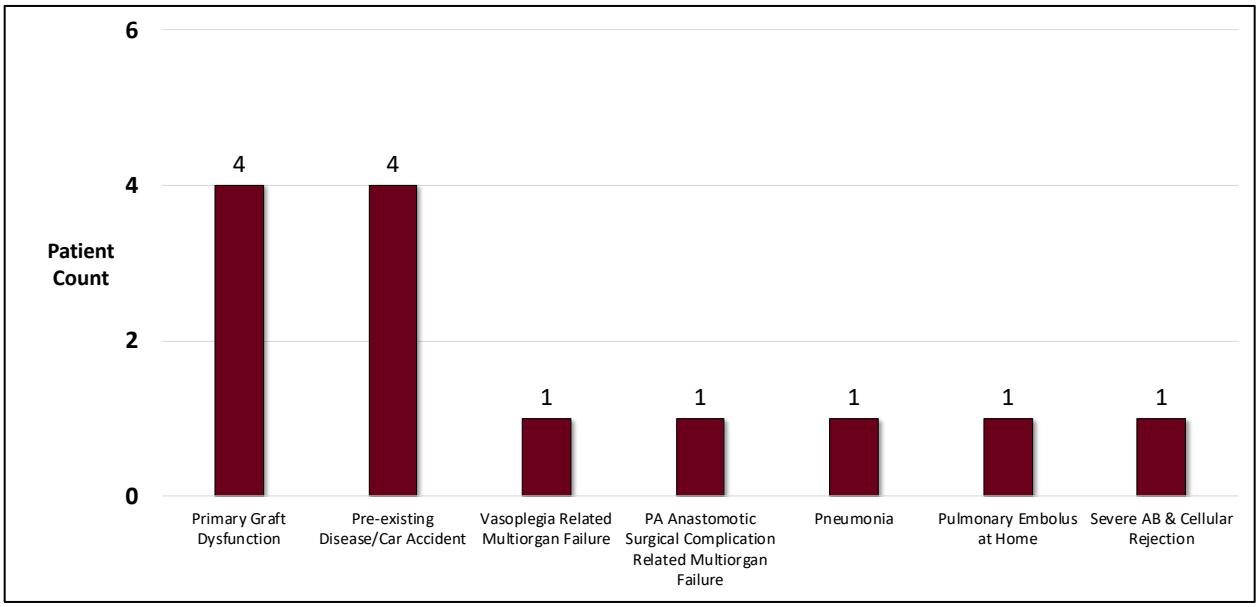
Follow-up Timepoint	Month 0	Month 1	Month 6	Month 12	Month 18	Month 24
Overall	75	70	65	59	50	30
Cardiac Related	75	70	65	59	50	30

The causes of death for EXPAND subjects through 14 months post-transplant are illustrated in Figure 10 below. It is important to consider that 4 of 13 deaths in the OCS Heart EXPAND trial through 14 months (representing 5% of the overall mortality in the trial) were due to recipient factors and were not related to the transplanted heart, in general, or the use of the OCS Heart System:

- 1 subject died on Day 29 due to pre-existing chronic liver cirrhosis.
- 1 subject died on Day 80 and the subject likely had undiagnosed parenchymal lung disease leading to post-op acute respiratory distress disease.
- 1 subject died on Day 212 due to re-occurrence of pre-existing amyloidosis with refractory GI bleed.
- 1 subject died 14 months post-transplant due to motor vehicle accident that is unlikely to be related the transplant procedure or the transplanted heart.

These deaths were related to the recipients' comorbidities or other extraneous factors and are not attributable to the heart transplant or the use of the OCS Heart System.

Figure 10: Causes of Death in the OCS Heart EXPAND Trial through 14 Months Post-transplant



15. Serious Adverse Events (SAEs)

Table 13 below shows the adjudicated SAEs by System Organ Class for OCS Heart EXPAND subjects. All SAEs were reviewed and adjudicated by the Medical Monitor.

Table 13: List of Adjudicated SAEs By System Organ Class and Preferred Term – Transplanted Recipient Population through 30 Days of Follow-up

System Organ Class	Preferred Term	Subjects N=75	Events
Total		56 (74.7%)	106 (100%)
Cardiac disorders		31 (41.3%)	38 (35.8%)
	Arrhythmia	4 (5.3%)	4 (3.8%)
	Arrhythmia supraventricular	1 (1.3%)	1 (0.9%)
	Atrial fibrillation	5 (6.7%)	5 (4.7%)
	Atrial flutter	1 (1.3%)	1 (0.9%)
	Atrial tachycardia	1 (1.3%)	1 (0.9%)
	Atrioventricular block	1 (1.3%)	1 (0.9%)
	Bradycardia	1 (1.3%)	1 (0.9%)
	Cardiac failure congestive	4 (5.3%)	4 (3.8%)
	Cor pulmonale	2 (2.7%)	2 (1.9%)
	Electromechanical dissociation	1 (1.3%)	1 (0.9%)
	Left ventricular dysfunction	5 (6.7%)	4 (4.7%)
	Left ventricular failure	1 (1.3%)	1 (0.9%)

System Organ Class	Preferred Term	Subjects N=75	Events
	Nodal rhythm	1 (1.3%)	1 (0.9%)
	Pericardial effusion	5 (6.7%)	5 (4.7%)
	Right ventricular dysfunction	4 (5.3%)	4 (3.8%)
	Right ventricular failure	1 (1.3%)	1 (0.9%)
Congenital, familial and genetic disorders		1 (1.3%)	1 (0.9%)
	Atrial septal defect	1 (1.3%)	1 (0.9%)
General disorders and administration site conditions		1 (1.3%)	1 (0.9%)
	Multi-organ failure	1 (1.3%)	1 (0.9%)
Hepatobiliary disorders		1 (1.3%)	1 (0.9%)
	Hepatic failure	1 (1.3%)	1 (0.9%)
Immune system disorders		12 (16.0%)	12 (11.3%)
	Heart transplant rejection	12 (16.0%)	12(11.3%)
Infections and infestations		4 (5.3%)	4 (3.8%)
	Clostridial infection	1 (1.3%)	1 (0.9%)
	H1N1 influenza	1 (1.3%)	1 (0.9%)
	Pneumonia	1 (1.3%)	1 (0.9%)
	Sepsis	1 (1.3%)	1 (0.9%)
Injury, poisoning and procedural complications		9 (12.0%)	10 (9.4%)
	Cardiac procedure complication	3 (4.0%)	3 (2.8%)
	Heart injury	1 (1.3%)	1 (0.9%)
	Operative haemorrhage	1 (1.3%)	1 (0.9%)
	Post-operative thoracic procedure complication	1 (1.3%)	1 (0.9%)
	Procedural complication	2 (2.7%)	2 (1.9%)
	Rectal laceration post-operative	1 (1.3%)	1 (0.9%)
	Vascular pseudoaneurysm	1 (1.3%)	1 (0.9%)
Metabolism and nutrition disorders		1 (1.3%)	1 (0.9%)
	Fluid overload	1 (1.3%)	1 (0.9%)
Nervous system disorders		6 (8.0%)	6 (5.7%)
	Cerebrovascular accident	3 (4.0%)	3 (2.8%)
	Convulsion	2 (2.7%)	2 (1.9%)

System Organ Class	Preferred Term	Subjects N=75	Events
	Vocal cord paralysis	1 (1.3%)	1 (0.9%)
Psychiatric disorders		3 (4.0%)	3 (2.8%)
	Delirium	3 (4.0%)	3 (2.8%)
Renal and urinary disorders		12 (16.0%)	12 (11.3%)
	Renal failure acute	10 (13.3%)	10 (9.4%)
	Renal impairment	2 (2.7%)	2 (1.9%)
Respiratory, thoracic and mediastinal disorders		14 (18.7%)	15 (14.2%)
	Acute respiratory distress syndrome	1 (1.3%)	1 (0.9%)
	Acute respiratory failure	2 (2.7%)	2 (1.9%)
	Hydrothorax	1 (1.3%)	1 (0.9%)
	Hypoxia	1 (1.3%)	1 (0.9%)
	Pleural effusion	3 (4.0%)	3 (2.8%)
	Respiratory distress	1 (1.3%)	1 (0.9%)
	Respiratory failure	6 (8.0%)	6 (5.7%)
Vascular disorders		2 (2.7%)	2 (1.9%)
	Hemorrhage	1 (1.3%)	1 (0.9%)
	Subclavian vein thrombosis	1 (1.3%)	1 (0.9%)

Notes: Number of subjects refers to the number of subjects with at least one serious adverse event of the indicated type. Number of events refers to all events of the indicated type. Percentages are calculated based on the total number of subjects in the Transplanted Recipient Population, or the total number of events, as appropriate. For number of subjects, subjects experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term.

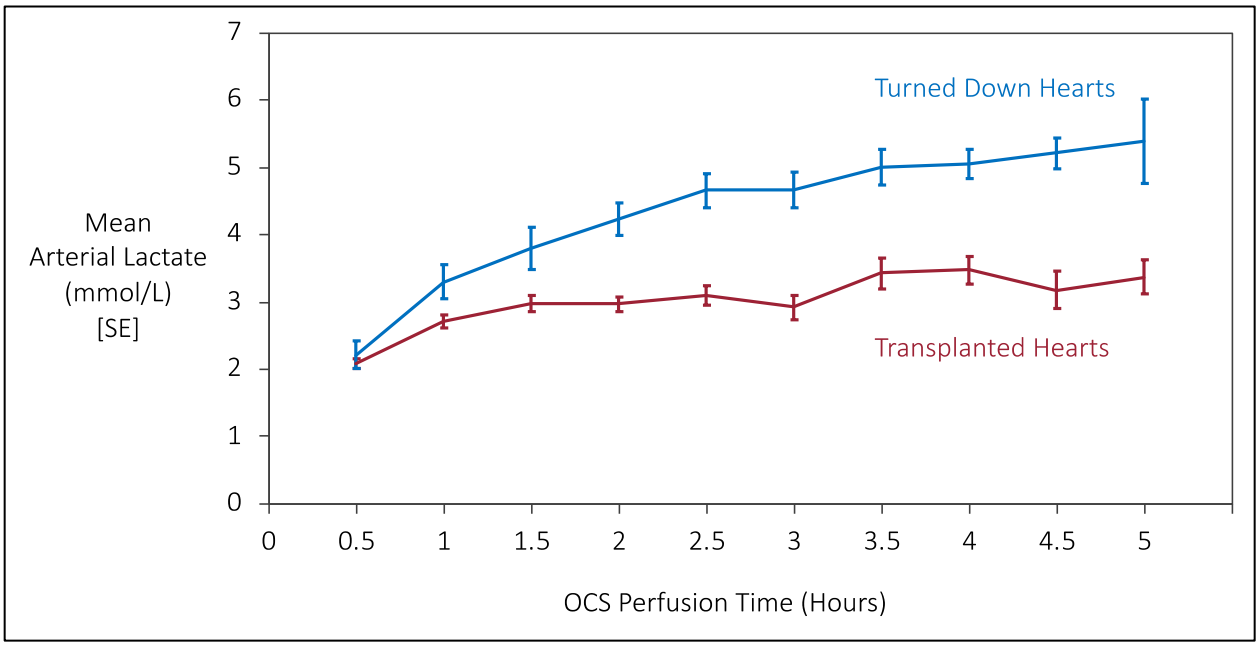
16. Analysis of Donor Hearts Turned Down following OCS Preservation

Of the 93 donor hearts instrumented on OCS, 18 donor hearts (matched to 16 subjects) did not meet transplantability criteria following preservation on OCS Heart System and were not transplanted and 75 of 93 donor hearts were successfully transplanted after OCS Heart System preservation and assessment (81% utilization rate). The mean UNOS donor match run refusals for the turned down hearts was 80.7, indicating that they most likely would not have been utilized outside of the Heart EXPAND trial. These turned down donor hearts exhibited unstable and rising lactate trends despite multiple attempts by the user to optimize perfusion parameters. Figure 11 below illustrates the mean lactate values for all 18 hearts that were turned down after OCS Heart System assessment as compared to the OCS Heart System lactate profile for the donor hearts that were transplanted in the OCS Heart EXPAND Trial. The disposition of the 16 recipients that were initially matched to these 18 turned down hearts were as follows:

- 12 patients were transplanted outside of the study with a second donor heart offer that was standard criteria and was preserved on cold storage.

- 1 patient was transplanted in the OCS Heart EXPAND trial with another donor heart preserved with OCS Heart System.
- 3 patients remained on the waiting list awaiting another donor heart offer. 1 of these 3 patients died on the waiting list while waiting for another donor heart offer and 2 patients were alive on the waiting list at the conclusion of the study.

Figure 11: Mean Arterial Lactate Trend on OCS Heart System for All Turned Down Donor Hearts Compared to Hearts that were Transplanted in EXPAND Trial



17. Conclusions of the OCS Heart EXPAND Trial

The results of the OCS Heart EXPAND trial provide ample assurance of effectiveness, safety and significant benefit/risk profile to support the OCS Heart System approval for the proposed clinical indication:

- An analysis of risk factors for donor hearts from the national UNOS/SRTR registry data demonstrated that the OCS Heart EXPAND trial enrolled donor hearts that are seldom or rarely transplanted in the U.S. today using ischemic cold storage. The use of the OCS Heart System resulted in successful transplantation of 81% of these types of donor hearts. This finding supports the benefit of the OCS Heart System to expand the donor pool to increase the number of heart transplants performed in the U.S.
- The OCS Heart EXPAND trial met its primary effectiveness composite endpoint of 30-day patient survival and freedom from severe ISHLT PGD with an 88% success rate on the primary effectiveness composite endpoint ($p<0.0001$).
- The 30-day survival in the OCS Heart EXPAND trial of 95% is comparable to contemporary standard criteria heart transplant survival in the U.S. (Colvin, et al., 2020).
- The incidence of severe ISHLT PGD post-transplant of 10.7% in the OCS Heart EXPAND trial is comparable to or lower than contemporary rates of severe heart PGD published in the literature.

- The OCS Heart EXPAND trial long-term patient survival at 6 and 12 months post-transplant was 88% and 84%, respectively. Post-hoc analysis of cardiac graft-related survival was 95% at 6 months and 12 months post-transplant, respectively.
- The OCS Heart EXPAND trial demonstrated the safety of the OCS Heart System. The mean number of HGRSAEs per patient was 0.2 ± 0.37 with an overall safety profile that was consistent with routine heart transplantation.
- Serious Adverse Events were typical for patients undergoing heart transplantation, and do not raise any signals for concern.

B. OCS Heart EXPAND and OCS Heart EXPAND Continued Access (CAP) pooled analysis population

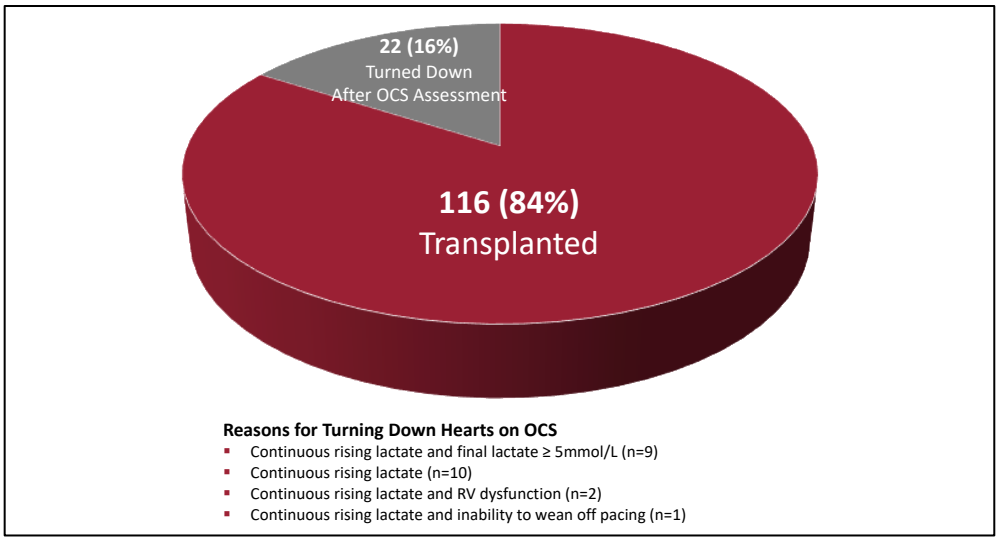
FDA approved a CAP for the OCS Heart EXPAND trial for an additional 75 patients. As of the date of database closure, in the OCS Heart EXPAND CAP, 49 donor hearts had been perfused on OCS, 45 patients have been transplanted and 41 of 45 of these transplanted recipients had a minimum of 30 days follow-up post-transplant with source data verified. Therefore, the analyses for transplanted recipients in this pooled analysis is based on these 41 patients and we also chose to present utilization rate based on these 41 patients for clarity and consistency.

This section presents a pooled analysis that combines the donor hearts and the transplanted recipients in the OCS Heart EXPAND trial with the donor hearts and transplanted recipients in the OCS Heart EXPAND CAP. This is appropriate since the OCS Heart EXPAND trial and the OCS Heart EXPAND CAP used the same protocol.

1. Donor Heart Utilization

As of the date of database closure, 138 donor hearts were perfused and assessed on the OCS Heart System in the combined OCS Heart EXPAND + CAP population. The utilization rate, as defined in the protocol, was 84.0%, with 116 of 138 extended criteria donor hearts successfully transplanted (Figure 12).

Figure 12: Donor Heart Utilization in OCS Heart EXPAND Trial and OCS Heart EXPAND CAP Pooled Analysis



This is a clinically important result, given that donor hearts were rejected by other centers and likely would not have been utilized outside of the OCS Heart EXPAND trial and OCS Heart EXPAND CAP. Table 14 below shows the donor match run data available from UNOS/SRTR for the combined OCS Heart EXPAND + CAP donor hearts which shows that these donor hearts were refused by other centers a mean of 59.7 times.

Table 14: UNOS Donor Match Run Donor Heart Offers Refusals Prior to Acceptance in OCS Heart EXPAND Trial and OCS Heart EXPAND CAP

	UNOS Donor Match Run Data for EXPAND & CAP Population N = 138
Mean number of Refusals per donor heart (Mean ± SD)	59.7 ± 90.8
Median number of Refusals per donor heart	22
Minimum - Maximum	0-480

2. Transplanted Recipient Population

As of the date of database closure, the transplanted recipient population consists of 116 subjects who were transplanted with donor hearts preserved on OCS and followed for a minimum of 30 days post-transplant. The analyses of all effectiveness and safety endpoints in the pooled cohort was based on the transplanted recipient population.

3. Recipients Demographic Characteristics and Risk Factors

The recipient demographics are shown in Table 15 below. The majority of recipients (64%) were UNOS Urgency Status 1A and were on mechanical circulatory support at the time of transplant (75%, 87/116).

Table 15: Summary of Recipient Characteristics for Combined OCS Heart EXPAND + CAP

Recipient Characteristics	**OCS Transplanted Recipients N=116**
Age (years) mean ± SD	54.3 ± 13.2
Age > 65 years	25/116 (21.6%)
Gender – male n (%)	93 (80.2%)
BMI (kg/m^2) – mean ± SD	28.3 ± 4.7
Race	
• Asian	2 (1.7%)
• Black or African American	24 (20.7%)
• Native Hawaiian or Other Pacific Islander	1 (0.9%)
• White	86 (74.1%)
• Other	2 (1.7%)
• Not Provided	1 (0.9%)
History of Mechanical Circulatory Support	87 (75.0%)

Recipient Characteristics	OCS Transplanted Recipients N=116
• LVAD	58 (50.0%)
• RVAD	1 (0.9%)
• BiVAD	1 (0.9%)
• ECMO	2 (1.7%)
• IABP	27 (23.3%)
• Artificial Heart	0 (0%)
Heart Allocation Status[1] n (%):	
• IA or High Urgent	77 (66.4%)
• IB or Urgent	34 (29.3%)
• II	5 (4.3%)
Primary Etiology of Heart Failure Diagnosis	
• Ischemic Cardiomyopathy	40 (34.5%)
• Congenital Heart Disease	5 (4.3%)
• Restrictive Cardiomyopathy	7 (6.0%)
• Non-ischemic Cardiomyopathy	39 (33.6%)
• Dilated Cardiomyopathy	16 (13.8%)
• Other	9 (7.8%)
Female donor to male recipient mismatch	12 (10.3%)
Renal dysfunction	12 (10.3%)
PRA (%) mean (range)	7.4 (0-81)
[1]UNOS had implemented a new allocation urgency status system between the time of the EXPAND trial and EXPAND CAP. In order to combine results, Status 1,2,3 = 1A, Status 4 = 1B and Status 5,6 = Status II	

4. Donor Characteristics and Risk Factors

Donor inclusion criteria/risk factors are provided in Table 16 below. Among these 116 transplanted recipients, 52 (44.8%) received donor hearts that met multiple donor inclusion criteria.

Table 16: Donor Inclusion Criteria Met for Transplanted Donor Hearts for OCS Heart EXPAND + CAP

Donor Inclusion Criteria Met n (%)*	OCS Transplanted Donors N=116
Expected Cross-Clamp Time ≥ 4hr	53/116 (45.7%)
Donor Age ≥ 55	12/116 (10.3%)
LVH	22/116 (19.0%)

Donor Inclusion Criteria Met n (%)*	OCS Transplanted Donors N=116
Downtime ≥ 20 min	33/116 (28.4%)
LVEF 40% -50%	27/116 (23.3%)
Luminal irregularities	10/116 (8.6%)
Alcoholism	16/116 (13.8%)
Carbon Monoxide as cause of death	1/116 (0.9%)
Diabetes	3/116 (2.6%)
Donor Age 45-55 with no coronary cath data	1/116 (0.9%)
Donors with Multiple Criteria	52/116 (44.8%)
* Donor inclusion criteria presented reflect additional review and verification of source documentation by TransMedics during PMA review.	

5. Comparison of Donor Characteristics and Risk Factors: OCS Heart EXPAND + CAP Pooled Population and UNOS/SRTR Standard Criteria Donor Hearts

An analysis of donor data from the national UNOS/SRTR database of standard criteria donors transplanted today using cold storage compared to the combined OCS Heart EXPAND + CAP population was performed.

For this analysis, the N=138 donor hearts in the OCS Heart EXPAND + CAP population are compared to 10,873 donor hearts transplanted over the time period of January 2015-March 2019, which excludes any recipients of OCS donor hearts.

Out of the 10,873 donor hearts preserved on cold storage over the time period from January 2015-March 2019, the UNOS/SRTR data indicated:

- Only 2% of the donor hearts had downtime ≥ 20 minutes
- Only 3% of the donor hearts had donor age ≥ 55
- Only 5% of the donor hearts had LVEF 40-50%,
- Only 4% of the donor hearts had a history of diabetes
- Only 16% of the donor hearts had cross-clamp time ≥4 hr
- Only 17% of the donor hearts had a history of alcoholism.

The data demonstrate that the EXPAND + CAP donors are not routinely transplanted on cold storage in the U.S. today. This is further demonstrated when considering donors transplanted in the U.S. on cold storage with two or more criteria (which comprised 45% of donor hearts in the EXPAND + CAP population). As shown in Table 17 below, of the 10,873 donor hearts preserved on cold storage:

- Only 5% of donor hearts had cross-clamp time ≥ 4 hrs and one other criterion (e.g., either downtime ≥ 20 min or alcoholism or diabetes or LVEF 40-50%).
- Only 1% of donor hearts had donor age ≥ 55 and one other criterion (e.g., either downtime ≥ 20 min or alcoholism or diabetes or LVEF 40-50%).

- Only 0.6% of donor hearts had downtime ≥ 20 minutes and one other criterion (e.g., either alcoholism, diabetes or LVEF 40-50%).

Table 17: Donor Characteristics for EXPAND + CAP Heart Population vs. UNOS/SRTR Hearts Transplanted 2015-March 2019

Donor Characteristics	Expand + CAP (N=138)	UNOS/SRTR (N=10,873)	p-value
Age (yr) – Mean ± SD	36.4 ± 12.1	32.1 ± 11.0	<0.0001
Age ≥ 55 - n (%)	13 (9.4%)	309 (2.8%)	0.0002
LV Ejection Fraction % - Mean ± SD	58.1 ± 8.4	61.7 ± 6.5	<0.0001
Cross-Clamp Time ≥ 4 Hours – n (%) (Expected)	66 (47.8%)	1730 (15.9%)	<0.0001
Cross-Clamp Time ≥ 4 Hours – n (%) (Actual)	113 (97.4%)	1730 (15.9%)	<0.0001
LVEF between 40% - 50% - n (%)	30 (21.7%)	500 (4.6%)	<0.0001
Down Time ≥ 20 Minutes – n (%)	43 (31.2%)	255 (2.3%)	<0.0001
Social History of Alcoholism – n (%)	17 (12.3%)	1831 (16.8%)	0.1701
History of Diabetes - n (%)	4 (2.9%)	397 (3.7%)	0.8202
a. Cross-Clamp Time ≥ 4 h and (Age (yr) ≥ 55 or Downtime ≥ 20 Min. or History of Alcoholism or History of Diabetes or LVEF 40-50%) – n (%)	23 (16.7%)	500 (4.6%)	<0.0001
b. Age (yr) ≥ 55 and (Downtime ≥ 20 Min. or History of Alcoholism or History of Diabetes or LVEF 40-50%) – n (%)	8 (5.8%)	111 (1.0%)	0.0001
c. Downtime ≥ 20 Min. and (History of Alcoholism or History of Diabetes or LVEF 40-50%) – n (%)	10 (7.2%)	61 (0.6%)	<0.0001

6. Donor Heart Preservation Characteristics and Critical Times

OCS perfusion time, total ischemic time and cross-clamp time are listed in Table 18 below for the 116 transplanted recipients in the combined analysis.

Despite the total cross-clamp time that averaged over 6 hours (381 minutes), the OCS Heart System significantly reduced the injurious ischemic time for the hearts to less than 2 hours (103 minutes). These results are clinically significant since they support the potential of the OCS Heart System to facilitate long distance procurement to maximize donor heart utilization for transplantation while minimizing the negative impact of ischemic time for the donor hearts.

Table 18: Preservation Characteristics for Donor Hearts for Combined OCS Heart EXPAND CAP and OCS Heart EXPAND Trial Cohort (N=116)

Parameter	OCS (N=116)
Cross-clamp Time (mins)[1]	116
Mean ± SD	381.3 ± 90.98

Parameter	OCS (N=116)
Median	375.0
Min.- Max.	173 - 682
Total Ischemic Time (mins)[2]	116
Mean ± SD	102.8 ± 22.41
Median	98.0
Min.- Max.	65 - 189
OCS Perfusion Time (mins)	116
Mean ± SD	278.5 ± 80.84
Median	278.0
Min.- Max.	100 - 532

[1]Cross-clamp time is the time from aortic cross-clamp application time in the donor to the PA cross-clamp removal time in the recipient (Out of body time).

[2]Total ischemic time for hearts preserved by OCS is the cross-clamp time minus OCS perfusion time.

7. OCS Heart System Perfusion Parameters

The OCS perfusion parameters are summarized in Table 19 below for both transplanted and turned down donor hearts.

Table 19: OCS Heart System Perfusion Parameters for Donor Hearts for Combined OCS Heart EXPAND Trial and OCS Heart EXPAND CAP

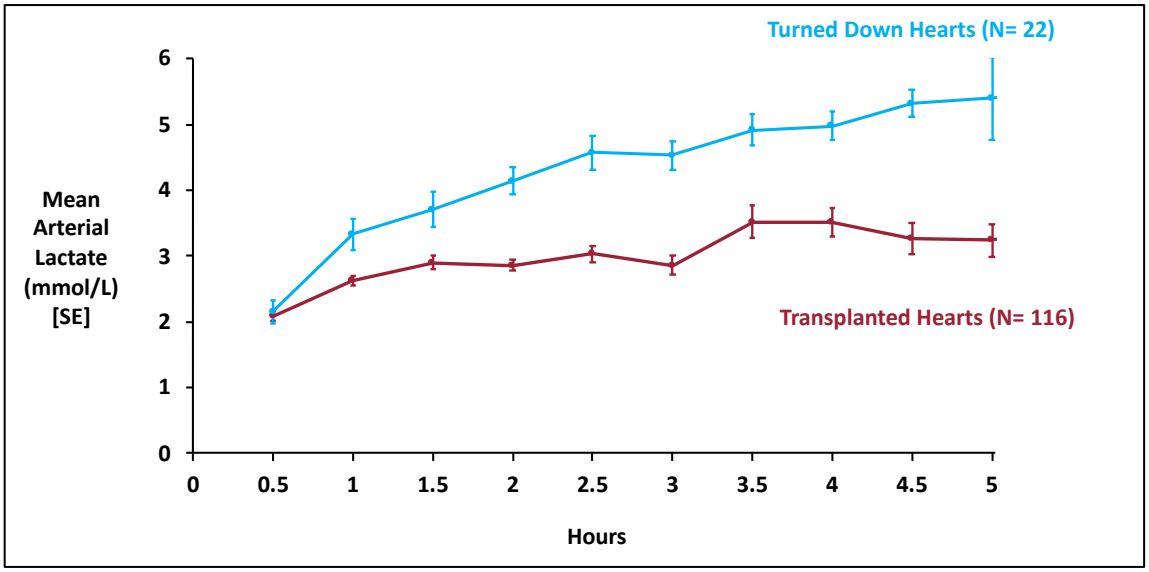
Parameter	OCS (N=116)	Turn Down (N=22)
Pump Flow Mean (L/min)		
N	116	22
Mean ± SD	1.119 ± 0.1141	1.143 ± 0.1110
Median	1.110	1.106
Minimum - Maximum	0.89 - 1.76	1.01 - 1.44
Coronary Flow Mean (L/min)		
N	116	22
Mean ± SD	0.749 ± 0.1284	0.744 ± 0.1650
Median	0.777	0.788
Minimum - Maximum	0.06 - 0.99	0.15 - 0.92
AOP Mean (mmHg)		
N	116	22
Mean ± SD	79.9 ± 8.23	82.1 ± 8.26
Median	80.9	83.4

Parameter	OCS (N=116)	Turn Down (N=22)
Minimum - Maximum	48 - 102	59 - 97
Initial Arterial Lactate (mmol/L)		
N	116	22
Mean ± SD	1.894 ± 0.7165	2.239 ± 0.9053
Median	1.735	2.000
Minimum - Maximum	0.67 - 5.70	1.06 - 4.47
Final Arterial Lactate (mmol/L)		
N	116	22
Mean ± SD	3.017 ± 1.0679	5.193 ± 1.0363
Median	2.835	4.885
Minimum - Maximum	0.55 - 7.59	3.50 - 7.89

Figure 13 below displays the average lactate trend for all donor hearts on the OCS Heart System that were accepted for transplantation in the OCS Heart EXPAND + CAP population compared to those that were turned down for transplantation. There was a substantial difference between the overall lactate trend of hearts that were transplanted vs. the hearts that were turned down after OCS Heart assessment.

It is important to recognize that lactate trend was only considered as a clinical indicator for adequacy of perfusion, after adjustment and optimization of OCS Heart perfusion parameters and hemodynamics. For many experienced OCS Heart clinical users, unstable and rising lactate trend despite multiple attempts to stabilize the perfusion parameters (CF and AOP) is a sign of compromised clinical condition of the donor heart which would lead them to turn down the heart for transplantation.

Figure 13: Mean Arterial Lactate Over Time in OCS Heart EXPAND + CAP Combined Transplanted Donor Hearts (N=116) vs. Turned Down Hearts (N= 22)



8. Primary and Secondary Endpoint Results

Table 20 below shows the results of the composite primary effectiveness endpoint for the combined OCS Heart EXPAND + CAP population. The primary effectiveness endpoint met the pre-specified objective performance goal of 65% with 91% of the subjects achieving success on the composite endpoint of patient survival at Day 30 post-transplantation and absence of severe ISHLT PGD in the first 24 hours post-transplantation.

The secondary endpoints are shown in Table 21. The 30-day survival of 96.5% in the combined OCS Heart EXPAND + CAP population is comparable to contemporary standard criteria heart transplant survival in the U.S (96%; Colvin, et al., 2020). The incidence of severe ISHLT PGD of 7.8% is lower than contemporary rates of severe heart PGD published in the literature.

The results demonstrate that these extended criteria hearts, those seldom used for transplant today, can be transplanted successfully with favorable post-transplant outcomes.

Table 20: Primary Effectiveness Endpoint for the Combined OCS Heart EXPAND + CAP Population

Results for Primary Endpoint Composite	**OCS (N= 116)**
Patient survival at day 30 post-transplantation and absence of severe PGD (left or right ventricle) in the first 24 hours post-transplantation	
Proportion (π1) (%) (n/N)	106/116 (91.4%)
95% CI (%) for Proportion2	(0.847, 0.958)

[1] π = n/N *100% = simple proportion.

[2] Clopper-Pearson exact confidence interval for a binomial proportion. Hypothesis test was not pre-specified for the combined analysis.

Table 21: Secondary Endpoint Results for the Combined OCS Heart EXPAND + CAP Population

Results for Secondary Endpoints (components of primary composite endpoint)	**OCS (N=116)**
Patient survival at day 30 post-transplantation	
Proportion (π^1) (%) (n/N)	111/115[3] (96.5%)
95% CI (%) for Proportion[2]	(0.913, 0.990)
Incidence of severe PGD (left or right ventricle) in the first 24 hours post-transplantation	
Proportion (π^1) (%) (n/N)	9/116 (7.8%)
95% CI (%) for Proportion[2]	(0.036, 0.142)

[1] π = n/N *100% = simple proportion.

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

[3] Excludes one subject with graft failure and re-transplant during the first 30 days

9. Donor Heart Utilization

In the combined OCS Heart EXPAND + CAP population, 116 of 138 donor hearts preserved on OCS were successfully transplanted (84% utilization rate as defined in the protocol). The turned down donor hearts exhibited unstable and rising lactate trends despite multiple attempts by the user to optimize perfusion parameters. Figure 13 above illustrates the mean lactate values for the 22 hearts that were turned down after OCS Heart System assessment in the combined OCS Heart EXPAND + CAP population as compared to the OCS Heart System lactate profile for the donor hearts that were transplanted.

10. Primary Safety Endpoint

The primary safety endpoint for the combined OCS Heart EXPAND + CAP population was 0.2 ± 0.37 (Table 22), which is the same as that observed in the OCS Heart EXPAND trial.

The incidence on moderate or severe PGD (LV or RV) was 15.5%, and one patient had primary graft failure requiring re-transplantation.

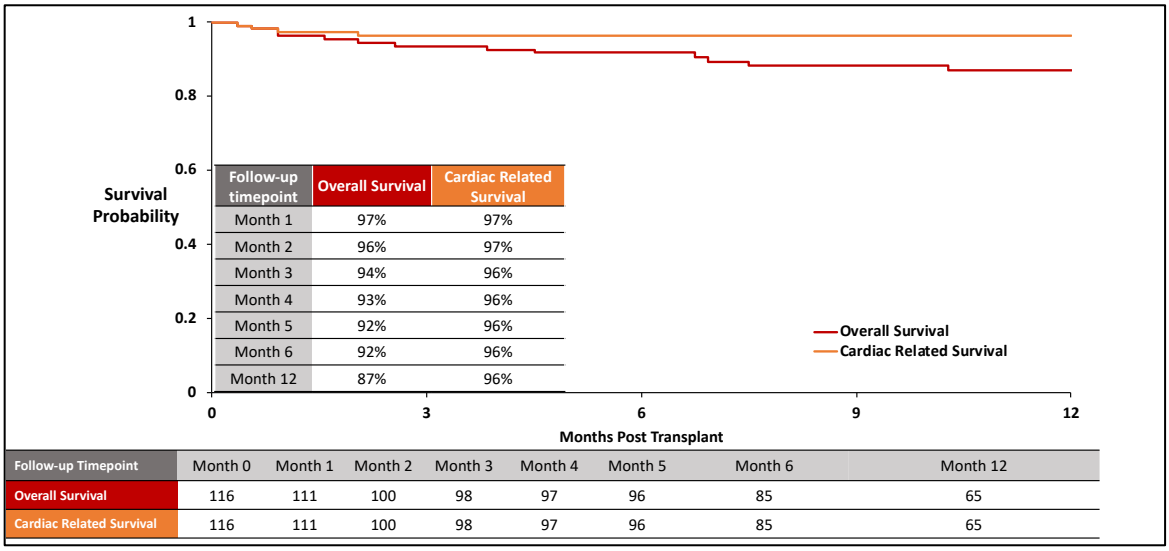
Table 22: Primary Safety Endpoint and Listing of HGRSAEs by Type for the Combined Cohort of OCS Heart EXPAND Trial and OCS Heart EXPAND CAP (N=116)

	OCS (N=116)
Number of HGRSAEs up to 30 days post-transplant	
Mean ± SD	0.2 ± 0.37
95% CI (%) for Mean	(0.1, 0.2)
HGRSAEs by Type	
Moderate or severe PGD (LV or RV), n/N (%)	18/116 (15.5%)
Primary Graft Failure requiring re-transplantation	1/116 (0.9%)

11. Patient Survival

Kaplan-Meier overall and cardiac graft-related patient survival for the combined OCS Heart EXPAND + CAP population (116 transplanted patients) is shown in Figure 14 below. Patient survival for OCS Heart EXPAND + CAP patients was 92% at 6 months, and 88% at 12 months. These results are comparable to contemporary rates reported in the UNOS registry for recipients of standard criteria donor hearts preserved on cold storage, i.e., 92% at 6 months and 90% at one year (Colvin, et al., 2020). Post-hoc analysis of cardiac graft-related survival was 96% at 6 and 12 months, respectively.

Figure 14: Overall Patient Survival and Cardiac Graft-related Survival for OCS Heart EXPAND Trial and OCS Heart EXPAND CAP Patients Combined through 12 Months Follow-up (N=116)



Follow-up timepoint	Overall Survival	Cardiac Related Survival
Month 1	97%	97%
Month 2	96%	97%
Month 3	94%	96%
Month 4	93%	96%
Month 5	92%	96%
Month 6	92%	96%
Month 12	87%	96%

Follow-up Timepoint	Month 0	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 12
Overall Survival	116	111	100	98	97	96	85	65
Cardiac Related Survival	116	111	100	98	97	96	85	65

12. Poolability Analyses

A site effect analysis based on the non-imputed data was conducted to assess the poolability of the combined OCS Heart EXPAND + CAP data for the primary effectiveness endpoint. For this analysis, sites with fewer than 5 subjects were grouped into a single, larger Analysis Site. A Fisher's exact test was performed to test the null hypothesis that the true proportion of transplanted patients meeting the primary effectiveness endpoint does not vary by site. A 0.15 significance level was used for this test. If the p-value <0.15, then an analysis adjusting for site will be considered. The p-value was 0.8418; therefore, no adjustment for site was needed.

13. Serious Adverse Events (SAEs)

Table 23 below shows the adjudicated SAEs by System Organ Class and Preferred term for the combined OCS Heart EXPAND + CAP population of N=116 transplanted recipients. The SAEs are typical of those experienced by heart transplant recipients and there are no signals of concern.

Table 23: List of Adjudicated SAEs By System Organ Class and Preferred Term – Transplanted Recipient Population through 30 Days of Follow-up in Combined OCS Heart EXPAND + CAP Population (N=116)

Status	Subjects (N=116) n (%)	Events n (%)
Total	82 (70.7%)	159 (100.0%)
Blood and lymphatic system disorders	1 (0.9%)	1 (0.6%)
Anaemia	1 (0.9%)	1 (0.6%)
Cardiac disorders	44 (37.9%)	54 (34.0%)
Arrhythmia	4 (3.4%)	4 (2.5%)
Arrhythmia supraventricular	1 (0.9%)	1 (0.6%)
Atrial fibrillation	8 (6.9%)	8 (5.0%)

Status	Subjects (N=116) n (%)	Events n (%)
Atrial flutter	1 (0.9%)	1 (0.6%)
Atrial tachycardia	1 (0.9%)	1 (0.6%)
Atrioventricular block	1 (0.9%)	1 (0.6%)
Atrioventricular block complete	2 (1.7%)	2 (1.3%)
Bradycardia	1 (0.9%)	1 (0.6%)
Cardiac failure congestive	4 (3.4%)	4 (2.5%)
Cor pulmonale	2 (1.7%)	2 (1.3%)
Electromechanical dissociation	1 (0.9%)	1 (0.6%)
Intrapericardial thrombosis	1 (0.9%)	1 (0.6%)
Left ventricular dysfunction	8 (6.9%)	8 (5.0%)
Left ventricular failure	1 (0.9%)	1 (0.6%)
Nodal rhythm	1 (0.9%)	1 (0.6%)
Pericardial effusion	5 (4.3%)	5 (3.1%)
Pericardial haemorrhage	1 (0.9%)	1 (0.6%)
Right ventricular dysfunction	7 (6.0%)	7 (4.4%)
Right ventricular failure	1 (0.9%)	1 (0.6%)
Sinus bradycardia	1 (0.9%)	1 (0.6%)
Ventricular dysfunction	2 (1.7%)	2 (1.3%)
Congenital, familial and genetic disorders	1 (0.9%)	1 (0.6%)
Atrial septal defect	1 (0.9%)	1 (0.6%)
General disorders and administration site conditions	1 (0.9%)	1 (0.6%)
Multi-organ failure	1 (0.9%)	1 (0.6%)
Hepatobiliary disorders	1 (0.9%)	1 (0.6%)
Hepatic failure	1 (0.9%)	1 (0.6%)
Immune system disorders	15 (12.9%)	15 (9.4%)
Heart transplant rejection	11 (9.5%)	11 (6.9%)
Transplant rejection	4 (3.4%)	4 (2.5%)
Infections and infestations	7 (6.0%)	7 (4.4%)
Bacteraemia	1 (0.9%)	1 (0.6%)
Clostridial infection	1 (0.9%)	1 (0.6%)
H1N1 influenza	1 (0.9%)	1 (0.6%)
Pneumonia	3 (2.6%)	3 (1.9%)
Sepsis	1 (0.9%)	1 (0.6%)

Status	Subjects (N=116) n (%)	Events n (%)
Injury, poisoning and procedural complications	10 (8.6%)	11 (6.9%)
Cardiac procedure complication	3 (2.6%)	3 (1.9%)
Heart injury	1 (0.9%)	1 (0.6%)
Operative haemorrhage	1 (0.9%)	1 (0.6%)
Postoperative thoracic procedure complication	1 (0.9%)	1 (0.6%)
Procedural complication	2 (1.7%)	2 (1.3%)
Rectal laceration postoperative	1 (0.9%)	1 (0.6%)
Vascular pseudoaneurysm	1 (0.9%)	1 (0.6%)
Vena cava injury	1 (0.9%)	1 (0.6%)
Metabolism and nutrition disorders	3 (2.6%)	3 (1.9%)
Dehydration	1 (0.9%)	1 (0.6%)
Fluid overload	2 (1.7%)	2 (1.3%)
Nervous system disorders	9 (7.8%)	9 (5.7%)
Cerebrovascular accident	4 (3.4%)	4 (2.5%)
Convulsion	2 (1.7%)	2 (1.3%)
Haemorrhagic stroke	1 (0.9%)	1 (0.6%)
Neuralgia	1 (0.9%)	1 (0.6%)
Vocal cord paralysis	1 (0.9%)	1 (0.6%)
Psychiatric disorders	5 (4.3%)	5 (3.1%)
Delirium	5 (4.3%)	5 (3.1%)
Renal and urinary disorders	22 (19.0%)	22 (13.8%)
Renal failure acute	19 (16.4%)	19 (11.9%)
Renal impairment	3 (2.6%)	3 (1.9%)
Respiratory, thoracic and mediastinal disorders	18 (15.5%)	21 (13.2%)
Acute respiratory distress syndrome	1 (0.9%)	1 (0.6%)
Acute respiratory failure	2 (1.7%)	2 (1.3%)
Bronchial secretion retention	1 (0.9%)	1 (0.6%)
Hydrothorax	1 (0.9%)	1 (0.6%)
Hypoxia	1 (0.9%)	1 (0.6%)
Pleural effusion	6 (5.2%)	6 (3.8%)
Pulmonary oedema	1 (0.9%)	1 (0.6%)

Status	Subjects (N=116) n (%)	Events n (%)
Respiratory distress	1 (0.9%)	1 (0.6%)
Respiratory failure	7 (6.0%)	7 (4.4%)
Vascular disorders	7 (6.0%)	8 (5.0%)
Aortic dissection	1 (0.9%)	1 (0.6%)
Haematoma	1 (0.9%)	1 (0.6%)
Haemorrhage	2 (1.7%)	2 (1.3%)
Hypotension	1 (0.9%)	1 (0.6%)
Orthostatic hypotension	2 (1.7%)	2 (1.3%)
Subclavian vein thrombosis	1 (0.9%)	1 (0.6%)

Notes: Number of subjects refers to the number of subjects with at least one serious adverse event of the indicated type. Number of events refers to all events of the indicated type. Percentages are calculated based on the total number of subjects in the Transplanted Recipient Population, or the total number of events, as appropriate. For number of subjects, subjects experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term.

14. Conclusions

The results of the OCS Heart EXPAND trial and OCS Heart EXPAND CAP combined population analyses provide substantial evidence of the effectiveness, safety and favorable benefit/risk profile of the OCS Heart System and support approval of the device for the proposed clinical indication:

OCS Heart System Demonstrated Effectiveness:

- An analysis of risk factors for donor hearts from the national UNOS/SRTR registry data demonstrated that the OCS Heart EXPAND and CAP trials enrolled donor hearts that are seldom or rarely transplanted in the U.S. today using ischemic cold storage. The use of the OCS Heart System resulted in successful transplantation of 84% of these types of donor hearts. This finding supports the benefit of the OCS Heart System to expand the donor pool to increase the number of heart transplants performed in the U.S.
- The combined OCS Heart EXPAND + CAP population met the primary effectiveness composite endpoint of 30-day post-transplant patient survival and freedom from severe ISHLT PGD with a 91% success rate on the primary effectiveness composite endpoint.
- The 30-day patient survival of 97% in the combined OCS Heart EXPAND + CAP population is comparable to contemporary standard criteria heart transplant survival in the U.S. (96%; Colvin, et al., 2020).
- The incidence of severe ISHLT PGD of 7.8% in the combined OCS Heart EXPAND + CAP population is lower than contemporary rates of severe heart PGD published in the literature.
- The long-term overall patient survival at 6 and 12 months post-transplant in the combined OCS Heart EXPAND + CAP population was 92% and 87%, respectively. These results are comparable to contemporary overall patient survival rates reported in the UNOS registry for recipients of standard criteria donor hearts preserved on cold storage, i.e.,

92% at 6 months and 90% at one year (Colvin, et al., 2020). Post-hoc analysis of cardiac graft-related survival was 96% at 6 month and 12 months post-transplant, respectively.

OCS Heart System Demonstrated Safety:

- The combined OCS Heart EXPAND + CAP population demonstrated the safety of the OCS Heart System. The mean number of HGRSAEs per patient was 0.2 ± 0.37.
- Serious Adverse Events were typical for patients undergoing heart transplantation, and do not raise any signals for concern.

OCS Heart System Demonstrated Significant Clinical Public Health Benefit/Risk Value:

- End-stage heart failure is a major public health issue in the U.S. and the incidence is estimated at 650,000 patients annually (Mancini and Colombo, 2015). Heart transplantation is the treatment of choice for addressing end-stage organ failure due to its positive clinical outcomes and excellent quality of life (Stehlik, et al., 2012). Unfortunately, the availability of heart transplantation has been limited by the significant underutilization of DBD hearts due to the limitations of cold static storage. Approximately 7 out of every 10 donated DBD hearts go unutilized in the U.S. due to the limitations of cold storage.
- The use of the OCS Heart System has led to utilization (as defined in the protocol) of a substantial proportion of donor hearts that are seldom used for transplantation today. Simply stated, the OCS Heart EXPAND and OCS Heart CAP trials studied extended criteria donor hearts that are seldomly used for transplant in the U.S. today, and the use of OCS Heart System resulted in transplantation of 81% -84% of these extended criteria donor hearts with good post-transplant outcomes. The utilization of these extended criteria donor hearts using the OCS Heart System has the potential to more than double the annual number of donor hearts available for transplantation in the U.S. The benefits of this increase in the donor pool would be substantial and may enable more life-saving heart transplants to patients dying on the waiting list of end stage heart failure.

C. PROCEED II Trial

Historical clinical data in this PMA comes from the PROCEED II trial, conducted under approved IDE G060127. PROCEED II was the first trial designed to evaluate the OCS Heart System in standard criteria heart preservation for transplantation. PROCEED II was a randomized, prospective, non-inferiority, open-label, multi-center clinical trial that evaluated whether the clinical outcomes of patients undergoing heart transplantation with standard donor hearts preserved on the OCS Heart System were non-inferior to the outcomes of heart transplant recipients whose donor hearts were preserved using standard-of-care cold storage. PROCEED II was designed in 2006 and was the first trial of *ex-vivo* donor organ perfusion in the world and the first of the OCS Heart System. This study provided important learnings for the OCS Heart EXPAND trial. The results have been published in the Lancet (Ardehali, et al., 2015).

As described in Section C12 of this document, there are fundamental differences between the PROCEED II and OCS Heart EXPAND trials.

1. Primary Study Endpoint

The primary study endpoint was 30-day patient survival following transplantation with the originally transplanted heart and no mechanical circulatory assist device at Day 30.

2. Secondary Study Endpoints

The secondary study endpoints were:

- Incidence of serious cardiac (graft)-related adverse events, defined as those which are attributed to preservation injury of the donor heart in the first 30 days post-transplant: e.g., right ventricular dysfunction; left ventricular dysfunction; graft failure and myocardial infarction.
- Incidence of biopsy proven ISHLT (International Society for Heart and Lung Transplant) grade 2R (moderate) or 3R (severe) acute rejection on any of the surveillance endomyocardial biopsies as determined by the core pathology laboratory or clinically symptomatic rejection requiring augmentation of immunosuppressive therapy during the 30-day follow-up period.
- Length of intensive care unit (ICU) stay.

3. Study Populations for Analysis

The Per Protocol (PP) Population consisted of all patients randomized to their original group who were transplanted and had no major protocol violations. This was the primary analysis population for the study.

The ITT population included all randomized patients for whom it was determined at the donor site that there was a matching and eligible heart. In analyses based on the ITT population, patients were analyzed as randomized. The As-Treated (AT) Population consisted of all randomized recipients who received a donor heart preserved by either the OCS or standard cold storage technique, subsequent to randomization, and regardless of whether or not the subject received a donor heart according to the randomization assignment.

Analysis of the primary study effectiveness endpoint was based on the Per Protocol population and was also analyzed for all study populations. All secondary endpoints were analyzed using the AT population.

4. Subject Disposition

Of the 143 initially screened and randomized patients, 13 patients failed secondary screening/eligibility. Thus, 130 patients comprised the ITT Population, with 67 patients randomly assigned to the OCS Group and 63 patients randomly assigned to the standard cold storage group (Control Group). The As-Treated Population consisted of 128 randomized patients who received an OCS or Control donor heart, regardless of whether or not there was conformance with the randomization assignment, with 62 in the OCS Group and 66 in the Control group. The Per-Protocol Population comprised 121 randomized subjects who received a donor heart in conformance with the randomization assignment and had no major protocol violations, with 60 in the OCS Group and 61 in the Control Group.

5. Donor and Recipient Baseline Characteristics and Risk Factors

Donor and recipient demographics and risk factors for the OCS and control groups are shown in Table 24 below. The groups were generally well balanced for donor and recipient characteristics.

Table 24: Donor and Recipient Characteristics (As Treated Populations)

Recipient Characteristics	**OCS Group (N=62)**	**Control Group (N=66)**
Age (yr)	53.0 (20-71)	54.7 (20-76)
Age > 65	11 (17.4%)	18 (27.3%)
Male Sex	52 (83.9%)	48 (72.7%)
BMI (kg/m^2)	26.3 (17-41)	24.2 (16-38)
Clinical History of Diabetes	17 (27.4%)	17 (25.8%)
On VAD	18 (29%)	15 (22.7%)
Female Donor to Male Recipient	12 (19.4%)	12 (18.2%)
Diagnosis of Cardiomyopathy		
• Ischemic	23 (37.1%)	20 (30.3%)
• Idiopathic	7 (11.3%)	10 (15.5%)
• Dilated Cardiomyopathy	21 (33.9%)	23 (34.8%)
• Congenital Heart Disease	1 (1.6%)	1 (1.5%)
• Restrictive	2 (3.2%)	4 (6.1%)
• Other	7 (11.3%)	9 (13.6%)
UNOS Status • IA • IB • II	 44 (71.0%) 8 (12.9%) 10 (16.1%)	 51 (77.3%) 6 (9.1%) 9 (13.6%)
Donor Characteristics	**OCS Group (N=62)**	**Control Group (N=66)**
Age (yr)	36.2 (18-58)	34.0 (13-60)
Age ≥ 55 years	2 (3.2%)	3 (4.5%)
Male Sex	42 (67.7%)	47 (71.2%)
BMI (kg/m^2)	27.7 (18-44)	26.0 (15-45)
LVEF Mean (range)	60.6 (50-70)	62.0 (45-75)
Cause of Death		
• Anoxia	14 (22.6%)	14 (21.2%)
• Stroke/CVA	17 (27.4%)	18 (27.3%)
• Head Trauma	26 (41.9%)	28 (42.4%)
• Other	5 (8.1%)	6 (9.1%)

Data are mean (range) or number (%), P-values are from the two-sample t-test for continuous variables, testing for a difference in means between treatments, or from Fisher's Exact Test for categorical variables, testing for a difference between treatments in the proportions in each category.

6. Primary Endpoint Results

The study met its primary endpoint for all study populations, demonstrating that the OCS Heart System was non-inferior to Control preservation at the pre-specified 10% margin (Table 25).

Table 25: Primary Endpoint (30-Day Patient and Graft Survival and Absence of a Mechanical Assist Device at Day 30) for Various Study Populations

Study Populations	OCS Group	Control Group	Between Group Difference in %	95% Upper Confidence Bound for Difference in %	p-value*
Per Protocol	56/60 (93.3)	59/61 (96.7)	3.4	9.9	0.0469
As Treated	58/62 (93.5)	64/66 (97.0)	3.5	9.6	0.0404
Intent to Treat[1]	63/67 (94.0)	61/63 (96.8)	2.8	8.8	0.0239

Data are number (%).

*The non-inferiority hypothesis was demonstrated for all three analysis populations as the 95% UCB for the difference between the two trial groups was < 10% for all populations.

[1] Missing values were imputed with multiple imputation. The logistic regression method of imputation was used with terms for treatment, age, and gender.

7. Secondary Endpoint Results – Cardiac Graft-related Serious Adverse Events

The study met the secondary endpoint of cardiac graft-related serious adverse events, demonstrating the safety of the OCS for donor heart preservation (non-inferiority of OCS compared with Control). Eight (8) OCS patients and 9 Control patients experienced one or more cardiac graft-related serious adverse events (Table 26).

Table 26: Secondary Endpoint – Patients Experiencing At Least One Cardiac Graft-related Serious Adverse Event (CEC-adjudicated)

Study Populations	OCS Group (N=62)	Control Group (N=66)	Between Group Difference in %	95% Upper Confidence Bound for Difference in %	p-value*
As Treated	8/62 (12.9)	9/66 (13.6)	0.7	9.1	0.0368

Data are number (%).

*The non-inferiority hypothesis was demonstrated as the 95% UCB for the difference between the two trial groups was < 10%.

8. Turned Down Donor Hearts Preserved on OCS

During the conduct of PROCEED II trial, five donor hearts treated with OCS preservation were deemed not acceptable for transplantation while on the OCS and were turned down for transplantation. Four (4) of the 5 donor hearts were declined due to rising perfusate lactate levels during the OCS preservation session, indicating persistent myocardial ischemia despite attempts to optimize myocardial perfusion. One heart was declined due to friable aortic tissue that made

it difficult to support the aorta cannula for OCS perfusion. It is important to note that all 5 turned down hearts were examined by independent cardiac transplant pathology core lab, and 3 out of the 5 hearts had significant chronic anatomical abnormalities completely unrelated to the OCS Heart preservation. The remaining 2 hearts had evidence of injuries consistent with cause of death and un-related to the OCS Heart preservation.

The ex-vivo metabolic assessment using lactate levels afforded by OCS is a new capability that enables metabolic data to be assessed by the transplant team up to the point of transplantation, which cannot be done using standard of care cold storage.

9. Summary of Patient Deaths in PROCEED II

There were 6 deaths in the OCS arm and 2 deaths in the control arm during the first 60 days post-transplant. The causes of death among these 8 patients were:

- Primary graft failure/dysfunction requiring ECMO - 1 OCS and 1 Control
- Cerebral Bleeding related - 1 OCS and 1 Control
- Severe vasoplegia post-transplant in a recipient with pre-transplant VAD support - 1 OCS
- Severe protamine reaction in a patient who experienced acute allergic reaction to FFP administration on CPB during the transplant procedure - 1 OCS
- Hyperacute rejection - 1 OCS
- Respiratory failure and sepsis secondary to preexisting COPD - 1 OCS.

10. Overall Adverse Events

The incidence of adverse events was similar between the OCS and Control groups, and there were no statistical differences between the two groups.

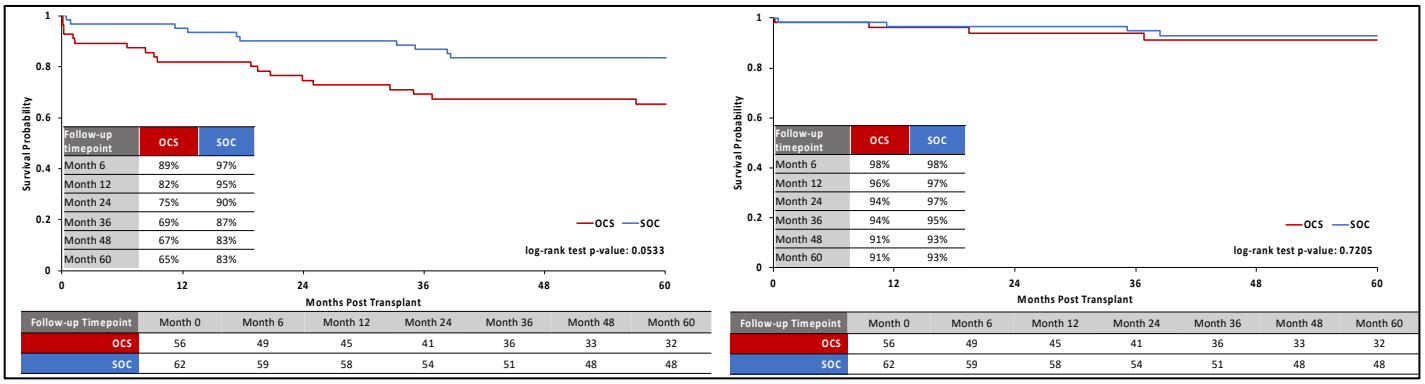
11. Unplanned Post-hoc Long-term Follow-up of PROCEED II Subjects Obtained through UNOS Heart Transplant Registry

The PROCEED II trial included 30-day post-transplant follow-up per the protocol. The FDA requested that the sponsor provide an unplanned post-hoc analysis of long-term outcome data for PROCEED II subjects from the UNOS heart transplant registry that extended beyond the 30-day follow-up.

The sponsor obtained unadjudicated long-term data on the U.S. patients enrolled in the PROCEED II from the UNOS registry through 5 years post-transplantation. Data were analyzed using the Kaplan-Meier method; patients who had not died were censored upon: (1) the last date which they were known to be alive via follow-up assessment or (2) the end of the period of analysis, whichever was earlier.

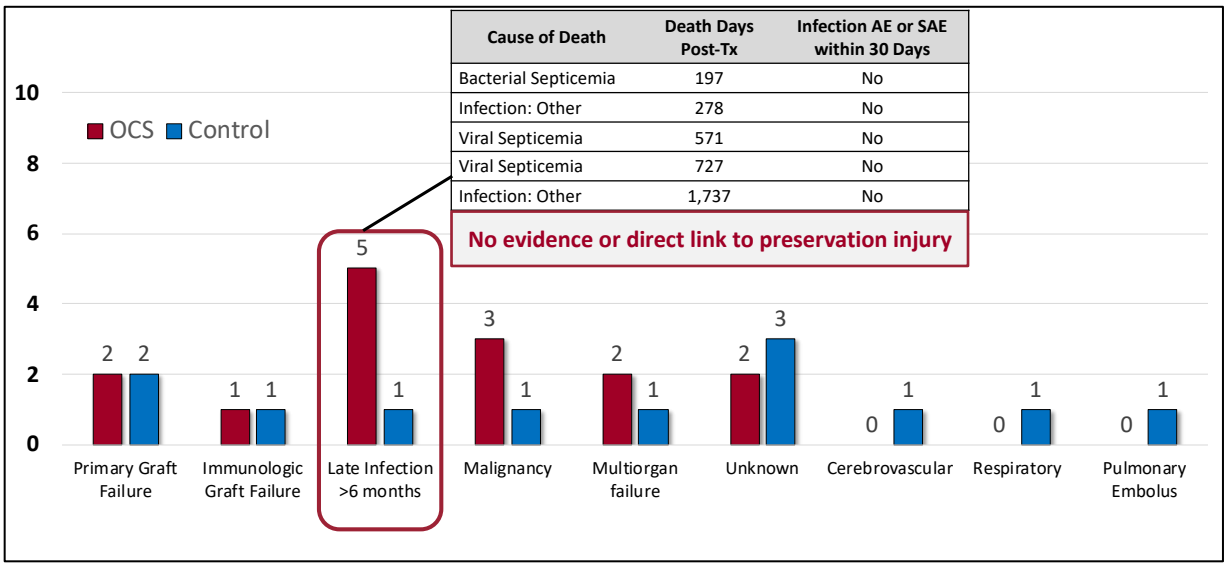
Post-hoc analysis of long-term survival data for PROCEED II subjects from the UNOS heart transplant registry demonstrated that the OCS arm had 19 deaths vs. 11 in the Control arm. The majority of this apparent difference in survival was not related to the cardiac graft. The number of patients whose cause of death was related to the cardiac graft (Non-immunologic or immunologic) was the same for the two groups (4 patients in the OCS Group and 4 in the Control Group) through 5 years (Figure 15).

Figure 15: PROCEED II Kaplan-Meier for Overall and Cardiac Related Survival through 5 Years Post-Transplant



When considering the causes of death for subjects who died > 60 days post-transplant, the higher number of deaths that occurred in the PROCEED II trial is primarily due to a higher incidence of late infection in the OCS arm compared to control (Figure 16).

Figure 16: Causes of Death for PROCEED II Subjects > 60 Days Post-transplant from UNOS Database



Using available UNOS data, there were 5 patients in the OCS group whose cause of death was Late Infection (> 180 days post-transplant); these patients died from a minimum of 197 days to a maximum of 1,737 days post-transplantation (Figure 16). None of these patients had an infection SAE or AE in the 30 days following transplant. Therefore, it is most likely that the infections were not associated with the preservation method, but rather with the immunosuppressed condition of these recipients. In addition, four patients died of Malignancy (3 in the OCS group and 1 in the Control group) which is consistent with the UNOS reported causes of deaths for adult heart transplant recipients in the U.S. and is often attributed to the immunosuppressed state of these recipients. Similar trends are reported for the UNOS registry in which infection and malignancy are among the leading causes of death post-transplantation among adult heart recipients (Colvin, et al, 2018).

There is no clear link to the OCS Heart System or the preservation period for the increased long-term mortality, based on the following facts:

- Cardiac-related mortality is similar between the two groups.
- Most of the long-term deaths were due to non-cardiac-related causes, typical of heart transplant recipients.
- All mortalities in the OCS group that occurred within the initial 60 days post-transplant had an uneventful OCS perfusion and preservation session with stable or declining lactate levels on OCS indicating adequate myocardial protection while on OCS.
- This discrepant mortality signal was not reported or observed in any published study for OCS clinical use for any donor heart criteria (standard, extended, and DCD donors). Rather, several peer-reviewed studies from single and multi-center clinical experience were published reporting better survival results for recipients of donor hearts preserved on the OCS Heart System from standard, extended criteria and even DCD donors (see Section D).

12. Differences between PROCEED II and OCS Heart EXPAND

It is important to recognize that the results from PROCEED II are less relevant to the current device and the indications for use. There are fundamental differences between the PROCEED II and OCS Heart EXPAND trials, as well as the differences in the OCS Heart System device design and clinical use models evaluated in the OCS Heart EXPAND and PROCEED II trials as summarized below.

- **Differences in Donor Heart Characteristics:** PROCEED II was a study of standard criteria donor hearts per the early 2000's standards, while the OCS Heart EXPAND trial is a study of extended criteria donor hearts based on 2014 contemporary DBD criteria, i.e., those that are seldom transplanted due to limitation of cold storage and that would benefit from OCS Heart System perfusion.

  These differences in donor characteristics and risk factors are further supported by the significantly different UNOS Donor Match Run data for PROCEED II that showed a mean of 11.8 refusals (median 2) prior to being accepted into the study compared to a mean of 65.6 (median 29) for the OCS Heart EXPAND trial (Table 27). These data show that donor hearts in the OCS Heart EXPAND trial were extended criteria and differed from the donor hearts in the PROCEED II trial.

Table 27: Comparison of UNOS Donor Match Run Data for OCS Heart EXPAND and PROCEED II Trials

Donor Heart Offers from UNOS donor match run data	**Heart EXPAND N = 93**	**PROCEED II N = 118**
Mean number of Refusals per donor heart (Mean ± SD)	65.6 ± 89.6	11.8 ± 31.7
Median number of Refusals per donor heart	29	2
Minimum - Maximum	0 - 379	0 - 296

- **Differences in OCS Heart System Design:** Following completion of the PROCEED II trial, two major device modifications were made and were implemented in the OCS Heart EXPAND trial in order to standardize management of the donor heart perfusion pressure and to minimize the impact of the user learning curve on the use of the OCS Heart System.
- **Differences in Post-OCS Heart Perfusion Myocardial Protection Protocol:** PROCEED II was the first pivotal trial conducted of the OCS Heart System and at the time that the protocol was designed and approved by the FDA, TransMedics and the trial investigators did not fully appreciate the importance of standardizing and controlling the myocardial protection protocol following OCS Heart perfusion after the heart had been removed from OCS. These aspects of the clinical use model were standardized across all investigational sites in the OCS Heart EXPAND trial and OCS Heart EXPAND CAP and are standard practice in current commercial use of the OCS Heart System outside of the U.S.

In summary, OCS Heart PROCEED II and OCS Heart EXPAND trials had different objectives and were conducted over different time periods. This led to differences in the trial design, donor hearts preserved and transplanted, and recipient risk profiles as well as important differences in aspects of the device design and the clinical use model. These substantive differences limit the applicability of data from the PROCEED II trial in consideration of the OCS Heart System for the clinical indications. Peer-reviewed published real-world experience with the OCS Heart System OUS (discussed in Section D below) in standard, extended and DCD donor heart criteria, as well as the results of the OCS Heart EXPAND trial and OCS Heart EXPAND CAP in the U.S. with extended-criteria donor hearts provide substantial evidence for the safety and effectiveness of the OCS Heart System for the proposed indication.

D. Summary of Published Literature Supporting the Safety of the OCS Heart System

There have been several peer-reviewed publications summarizing clinical studies of the OCS Heart System performed outside the U.S., including studies of DCD hearts (Table 28). It is important to note that the observational finding of increased mortality in the PROCEED II trial was not observed in any other study. Long-term survival for patients who received OCS-preserved donor hearts, with follow-up from one to five years, ranged from 86% to 100%, despite the fact that these studies utilized extended criteria and DCD donors. These data provide additional support for the finding that cardiac-related deaths were similar between the two groups in the PROCEED II study through 5 years, and that the imbalance in long-term overall survival was attributable to non-preservation-related causes.

Table 28: Summary of Published Studies of the OCS Heart System from 2014-2019

References	Study Design	Results
Koerner, et al. 2014	Prospective, nonrandomized, comparison of OCS (N=29) and cold storage (N=130) Primary endpoint was patient survival at 30 days, 1 and 2 years post-transplant. Secondary endpoints were primary and chronic allograft failure, noncardiac complications and length of hospital stay.	Two-year survival for OCS =89% vs 79% for cold storage Primary graft failure for OCS=6.9% vs 15.3% for cold storage Severe acute rejection – OCS=17% vs 23% for cold storage.

References	Study Design	Results
		Acute renal failure – 10% for OCS 25% for cold storage Length of hospital stay – 28 days for OCS vs 26 days for cold storage
Tsui, et al. 2015	Retrospective matched control comparison of OCS (N=19) vs cold storage control (N=24)	Survival at 1.5 years OCS =90% vs 83% for cold storage
Messer, 2017	Single-center observational matched cohort study comparing consecutive patients who received transplants of DCD donor heart between February 1, 2015, and March 31, 2017, vs matched recipients who received transplants of DBD donor hearts between February 1, 2013, and March 31, 2017. DCD Hearts on OCS (N=26) vs DBD Hearts on Cold storage (N=26)	Survival at 90 days: OCS/DCD – 92% vs Cold Storage/DBD – 96% Survival at one year: OCS/DCD – 86%, Cold Storage/DBD – 88%
Garcia Saez, 2016 and 2017	DCD hearts on OCS with High-risk recipients (N=7)	86% Survival for OCS with mean 324 days follow-up
Sponga, et al. 2019	Single center experience Extended Criteria Donors, OCS (N=17), Cold storage (N=70)	30-day survival – 100% OCS vs 94% for cold storage 1-year survival –100% OCS vs 82% for cold storage 5-year survival – 100% OCS vs 73% for cold storage
Rojas, et al., 2019	Prospective registry study at two sites. OCS (N=44) vs Cold Storage (N=82)	Ventilation time 7.1 days OCS vs 17.6 days for cold storage ICU stay 14.2 days OCS vs 24.7 days cold storage Post-operative ECMO 18.2% for OCS vs 28.4% for cold storage 30-day survival – 99.6% for OCS vs 91.2% cold storage One-year survival for OCS =88.6% vs 78.2% for cold storage
Chew, et al., 2019	23 DCD heart transplants on OCS	Four-year survival = 95%

XI. PEDIATRIC EXTRAPOLATION

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

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

TBD

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Preclinical Studies

TransMedics has performed a series of preclinical studies to demonstrate the OCS Heart System meets its performance specifications and that it is safe and effective for the proposed intended use. Preclinical testing included sterilization and shelf life, biocompatibility, software, electrical safety and EMC, engineering bench testing and animal functional testing. The testing demonstrates that the OCS Heart System meets its specifications.

B. Effectiveness Conclusions

- An analysis of risk factors for donor hearts from the national UNOS/SRTR registry data demonstrated that the OCS Heart EXPAND and OCS Heart EXPAND CAP trials enrolled donor hearts that are seldom or rarely transplanted in the U.S. today using ischemic cold storage. The use of the OCS Heart System resulted in successful transplantation of 81% and 84% of these types of donor hearts. This finding supports the benefit of the OCS Heart System to expand the donor pool to increase the number of heart transplants performed in the U.S.
- The OCS Heart EXPAND trial met its primary effectiveness composite endpoint of 30-day post-transplant patient survival and freedom from severe ISHLT PGD with an 88% success rate on the primary effectiveness composite endpoint ($p<0.0001$). The combined OCS Heart EXPAND + CAP population (N=116) met the primary effectiveness composite endpoint of 30-day post-transplant patient survival and freedom from severe ISHLT PGD with an 91% success rate on the primary effectiveness composite endpoint.
- The 30-day patient survival of 95% in the OCS Heart EXPAND trial is comparable to contemporary standard criteria heart transplant survival in the U.S. The 30-day patient survival of 97% in the combined OCS Heart EXPAND + CAP population is also comparable to contemporary standard criteria heart transplant survival in the U.S. (96%; Colvin, et al., 2020).
- The incidence of severe ISHLT PGD was 10.7% in the OCS Heart EXPAND trial and 7.8% in the combined OCS Heart EXPAND + CAP population. These rates are comparable to or lower than contemporary rates of severe heart PGD reported in the literature.
- The OCS Heart EXPAND trial long-term patient survival at 6 and 12 months post-transplant was 88% and 84%, respectively. Post-hoc analysis of cardiac graft-related survival was 95% at 6 months and 12 months post-transplant, respectively. The long-term patient survival at 6 and 12 months post-transplant in the combined OCS Heart EXPAND + CAP population was 92% and 87%, respectively. Post-hoc analysis of cardiac graft-related survival for the combined OCS Heart EXPAND + CAP population

was 96% at 6 month and 12 months post-transplant, respectively. The overall patient survival results are comparable to contemporary overall patient survival rates reported in the UNOS registry for recipients of standard criteria donor hearts preserved on cold storage, i.e., 92% at 6 months and 90% at one year (Colvin, et al., 2020).

- There was an overall survival difference observed in the PROCEED II RCT based on an unplanned, post-hoc analysis of unadjudicated data from the UNOS national heart transplant registry. However, this finding is of lesser importance in assessing the effectiveness and safety of the OCS Heart System for the proposed indication because of the following:
  - The proposed indication for use in this PMA is based on the specific categories of donor hearts studied in the OCS Heart EXPAND and OCS Heart EXPAND CAP trials and does not include the hearts that were the subject of PROCEED II trial.
  - The PROCEED II trial differs substantially from the OCS Heart EXPAND trial which makes it clinically less relevant to the assessment of the OCS Heart proposed indication:
    - There are donor and recipient characteristics that were significantly different between PROCEED II and OCS Heart.
    - There were major differences in the devices and use models evaluated in the PROCEED II and the OCS Heart EXPAND trials.
  - While an overall long-term survival difference is observed in PROCEED II, the cardiac graft-related mortality through 5 years post-transplant was similar between the OCS and control arms, based on 30-day follow-up data from PROCEED II and the causes of death recorded on long-term follow-up in the UNOS registry.
  - The observed difference in the PROCEED II RCT has not been reported or observed in any published study for OCS clinical use for any donor heart criteria (standard, extended, and DCD donors). Several peer-reviewed studies from different single and multi-center clinical experiences were published reporting better survival results for recipients of donor hearts preserved on the OCS Heart System from standard, extended criteria and even DCD donors.

C. Safety Conclusions

- The OCS Heart EXPAND trial demonstrated the safety of the OCS Heart System. The mean number of HGRSAEs per patient was 0.2 ± 0.37. The same result was observed for combined OCS Heart EXPAND + CAP population, with a mean number of HGRSAEs per patient of 0.2 ± 0.37.
- Serious Adverse Events were typical for patients undergoing heart transplantation, and do not raise any signals for concern.
- The sponsor developed and implemented a comprehensive clinical training program that includes extensive hands-on training and a point of use proprietary iOS application with detailed step by step instructions checklists and training videos. The sponsor also maintains 24 X 7 phone support to minimize users' learning curve and ensure proper use of the OCS to maximize safety for the patients.

D. Benefit-Risk Determination

- End-stage heart failure is a major public health issue in the U.S. and the incidence is estimated at 650,000 patients annually (Mancini and Colombo, 2015). Heart transplantation is the treatment of choice for addressing end-stage organ failure due to its positive clinical outcomes with excellent quality of life (Stehlik, et al., 2012). Unfortunately, heart transplant has been limited by the significant underutilization of DBD hearts due to the limitations of cold static storage. Approximately 7 out of every 10 donated DBD hearts go unutilized in the U.S. due to the limitations of cold storage.
- The use of the OCS Heart System has led to utilization (as defined in the protocol) of a substantial proportion of donor hearts that are seldom used for transplantation today. Simply stated, the OCS Heart EXPAND and OCS Heart EXPAND CAP trials studied extended criteria donor hearts that are seldomly used for transplant in the U.S. today and the use of OCS Heart System resulted in transplantation of 81% - 84% of these extended criteria donor hearts with good post-transplant outcomes. The utilization of these extended criteria donor hearts using the OCS Heart System has the potential to more than double the number of donor hearts available for transplantation in the U.S. The benefits of this increase in the donor pool would be substantial and could enable more life-saving heart transplants to patients dying on the waiting list of end stage heart failure.

E. 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.

XIV. CDRH DECISION

CDRH issued an approval order on [DATE].

The applicant's manufacturing facilities were previously inspected for the OCS Lung System PMA (P160013) and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820). Accordingly, FDA determined that a pre-approval inspection for this PMA was not required.

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

Ardehali, et al. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicenter, randomized non-inferiority trial. *Lancet.* 2015; 385: 2577-2584.

Baran, et al. What Number Are We? Donor Sequence and Outcomes of Heart Transplantation. *Circulation: Heart Failure.* 2019, 12(5): 1-9.

Chew, et al. Outcomes of Donation After Circulatory Death Heart Transplantation in Australia. *Journal of the American College of Cardiology*; Vol 73, No.12, 2019.

Colvin, et al. OPTN/SRTR 2016 Annual Data Report: *Heart. Am. J. Transplant*., 2018, https://doi.org/10.1111/ajt.14561.

Colvin, et al. OPTN/SRTR 2018 Annual Data Report. Heart. *Am. J. Transplant.*, 2020, 20:340-426. https://doi.org/10.1111/ajt.15676

Garcia Saéz, et al. Heart Transplantation after donor circulatory death in patients bridged to transplant with implantable left ventricular assist devices. *J. Heart Lung Transplant.;* 2016, 35(10): 1255-1260.

Garcia Saéz, et al. Donor Circulatory Death Heart Transplantation with Adverse Donor and Recipient Risk Profile. *J. Heart Lung Transplant*.; 2017, 36(45): S16.

Kobashigawa, et al. Report from a Consensus Conference on Primary Graft Dysfunction after Cardiac Transplantation. *J. Heart Lung Transplant*., 2014, 33(4):327-340.

Koerner, et al. Normothermic ex vivo allograft blood perfusion in clinical heart transplantation. *The Heart Surgery Forum.* 2014: 17: 141-145.

Mancini, D. and Colombo, P.C. Left Ventricular Assist Devices: A Rapidly Evolving Alternative to Transplant. J. Am. Col. Cardiol. 2015, 65(23): 2542-2545.

Messer, et al. Outcome after heart transplantation from donation after circulatory-determined death donors. *The Journal of Heart and Lung Transplantation*; Vol 36, No 12, December 2017.

Rojas, et al. Cardiac Transplantation in Higher Risk Patients: Is Ex Vivo Heart Perfusion a Safe Preservation Technique? A Two Center Experience. *The Journal of Heart and Lung Transplantation*; Vol 38, No 4, April 2019.

Sorabella, et al. Cardiac Donor Risk Factors Predictive of Short-Term Heart Transplant Recipient Mortality: An Analysis of the United Network For Organ Sharing. *Transplant Proc.* 2015 December; 47(10): 2944–2951.

Sponga, et al. Ex-vivo Perfusion on Marginal Donors in Transplantation: Clinical Results and Findings. *The Journal of Heart and Lung Transplantation*; Vol 38, No 4, April 2019.

Stehlik, et al. The Registry of the International Society for Heart and Lung Transplantation: 29th Official Adult Heart Transplant Report-2012; *The Journal of Heart and Lung Transplantation*, Vol 31, No 10, October 2012.

Trivedi, et al. Heart Transplant Survival Based on Recipient and Donor Risk Scoring: A UNOS Database Analysis. *ASAIO J.* 2016; 62:297-301.

Tsui, S., Private communication, 2015.