FDA Executive Summary

Prepared for the
April 6, 2021 virtual meeting of the
Circulatory System Devices Panel

(b)(4)

TransMedics, Inc., Andover, MA

TransMedics® Organ Care System™ (OCS) Heart System

Office of Cardiovascular Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
Food and Drug Administration

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1. Introduction

The purpose of this summary is to present information related to the safety and effectiveness of the TransMedics® Organ Care System™ Heart System (OCS Heart or OCS Heart System) manufactured by TransMedics, Inc. This device is designed to perfuse and maintain extended-criteria (also known as expanded-criteria) donor hearts in a temperature controlled (34°C), near-physiologic and beating state, during the time between cardioplegic arrest and retrieval, and repeat cardioplegic arrest and implantation into a suitable transplantation recipient.

Two pivotal studies and a continued access protocol (CAP) were conducted with the OCS Heart System under investigational device exemption (IDE): PROCEED II (G060127) and EXPAND (G140111).

- PROCEED II (G060127) was a randomized trial conducted between March 2009 and October 2013 with standard-criteria donor hearts. Donor hearts were randomized (1:1) to the OCS Heart System or standard-of-care (SOC, control) cold static preservation. (b)(4) was submitted to FDA for approval for standard-criteria donor hearts (b)(4)

- EXPAND (G140111) was a single arm study conducted between September 2015 and March 2018 with extended-criteria donor hearts (i.e., hearts that may not be considered standard criteria donor organs for one or more reasons). EXPAND was designed to leverage the results of PROCEED II and allow for an indication for use in non-standard criteria donor hearts. An EXPAND Continued Access Protocol (EXPAND CAP or "CAP") was approved on February 7, 2019 (G140111/S029) to permit continued use of the OCS Heart System while the PMA (b)(4)) was under review. Considered an adjunctive dataset, EXPAND CAP data for 41 transplanted hearts (and 4 turned-down hearts) were provided to FDA informally, between August 31, and December 4, 2020 for review (provided formally on January 22, 2021 under (b)(4)).

FDA considered the clinical data from both studies (G060127 and G140111) to evaluate the safety and effectiveness of the OCS Heart System. An Advisory Panel is being convened to discuss the clinical data that were collected in these studies in support of marketing approval for this device.

The Executive Summary for this Advisory Committee Meeting of the Circulatory System Devices Panel on the OCS Heart System for extended-criteria hearts includes the non-clinical and clinical data that has been provided by the sponsor in its PMA ((b)(4)) application. In particular, the clinical sections:

- Provide foundational information about the OCS Heart System used in the PROCEED II randomized trial for standard-criteria donor hearts;
- Summarize the EXPAND study design, results, and conclusions derived from the use of the OCS Heart System for extended-criteria donor hearts;
- Provide a summary of FDA's evaluation of the device's safety and effectiveness data; and
- Discuss the Agency's concerns regarding this PMA application and the EXPAND study data, including the:

- Robustness of the collected data;
- Possible deleterious effects to donor hearts associated with OCS Heart preservation;
- Observed mortality rate in recipients of donor organs preserved with the OCS Heart System;
- Heterogenous definition of "extended-criteria" donor hearts, the subjectivity of the donor heart inclusion criteria, and the potential for substantial overlap with standard-criteria donor organs;
- Potential use of the OCS Heart System for the standard-criteria heart donor pool; and
- Utility of heart lactate levels as a determinant of "transplantability" of procured donor hearts.

2. Proposed Indications for Use

TransMedics proposes the following indications for use statement for the OCS Heart System:

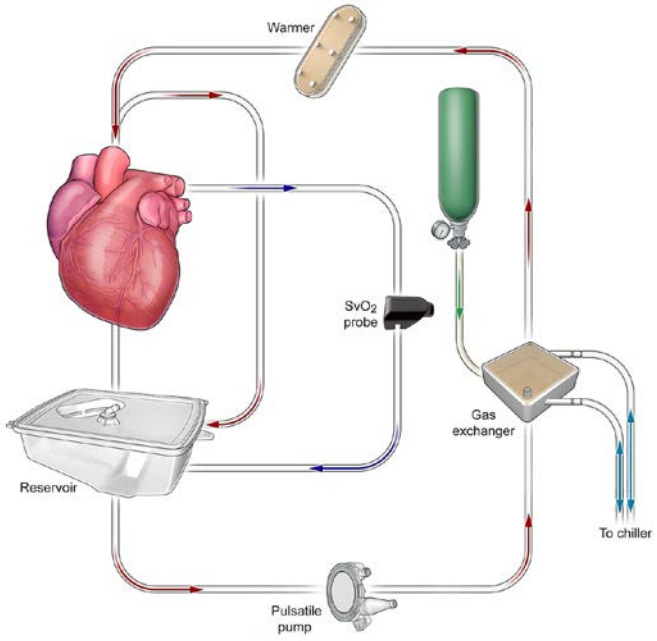
> The TransMedics® Organ Care System (OCS™) Heart System is a portable extracorporeal heart perfusion and monitoring system indicated for the resuscitation, preservation, and assessment of donor hearts in a near-physiologic, normothermic and beating state intended for a potential transplant recipient. 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 total cross-clamp time of ≥ 2 hours PLUS one of the following risk factors:
>   - 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 and ≤ 16 mm); or
>   - Donor angiogram with luminal irregularities but no significant coronary artery disease (CAD).

Panel: The Panel will be asked to comment on an appropriate indications for use statement that adequately defines the population of donor organs for which the device demonstrates a reasonable assurance of safety and effectiveness.

3. Device Description

The OCS Heart is a device designed to transport non-standard (i.e., "extended-criteria") donor hearts to the transplant recipient site by using extracorporeal circulation to maintain heart viability via continuous organ perfusion with temperature controlled, oxygenated blood (obtained from the donor) supplemented with the TransMedics' Heart Solution Set. The current standard-of-care (SOC) preservation method involves flushing the heart with a cold crystalloid cardioplegic solution, followed by cardiectomy, packing the heart in a sterile and hypothermic container, and transportation to the recipient's transplant center. SOC preservation aims to minimize the cold-ischemic time.

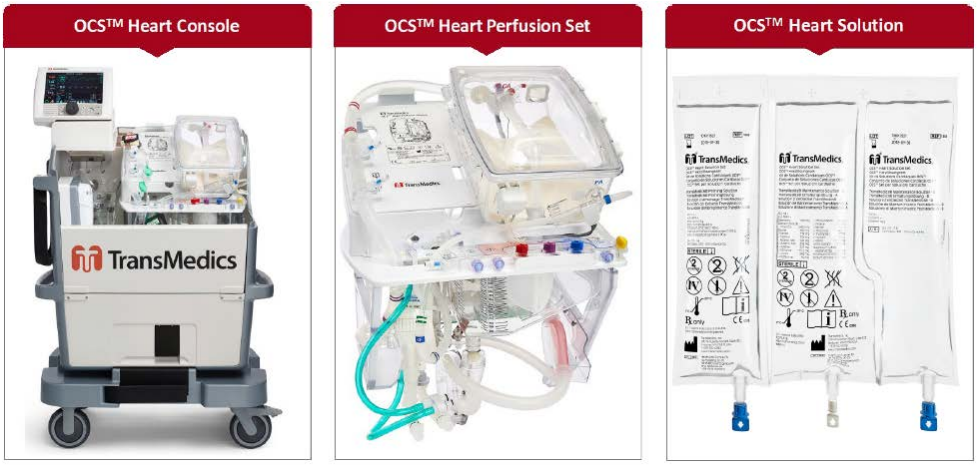
Figure 1: Schematic of OCS Fluid Flow



The TransMedics® OCS Heart System is composed of 3 major components:

- OCS Heart Console
- OCS Heart Perfusion Set (consists of the Heart Perfusion Module (HPM) and the Heart Perfusion Accessories)
- OCS Heart Solution

Figure 2: OCS Heart System Components



For a detailed description of the OCS Heart Console, the OCS Heart Perfusion Set (HPS) and the OCS Heart Solution Set and Solution Delivery Subsystem (SDS), please see Appendix A.

4. Principles of Operation

The OCS Heart circulates temperature-controlled (34°C) donor blood/OCS Solution through an oxygenator, to provide oxygen and nutrients to the donor heart during transportation of the donor organ to the recipient site. Throughout OCS support, the user can adjust blood flow rate, infusion rate, gas flow rate, and blood temperature in order to create an optimal perfusion environment for the donor organ, through direct measurements of aortic pressure (AOP), coronary flow (CF), and heart rate (HR). Lactate levels are measured and are used as an indicator of adequate myocardial perfusion of the donor organ throughout preservation. The perfusion parameters are monitored and adjusted as needed throughout the duration of support on the OCS Heart, with adjustments based on lactate levels and trends.

Instrumentation of Donor Heart

If the donor heart is deemed acceptable, the OCS Heart is assembled for use. Blood from the heparinized donor is collected (1100 – 1500 mL), passed through a leukocyte-depleting filter and into the reservoir of the HPM. The donor blood is supplemented with 500 mL of the OCS Priming Solution and mixed via the Heart Console pump. The pump circulates the perfusate through the circuit to prime and de-air the HPM, as well as activate gas flow and blood warming.

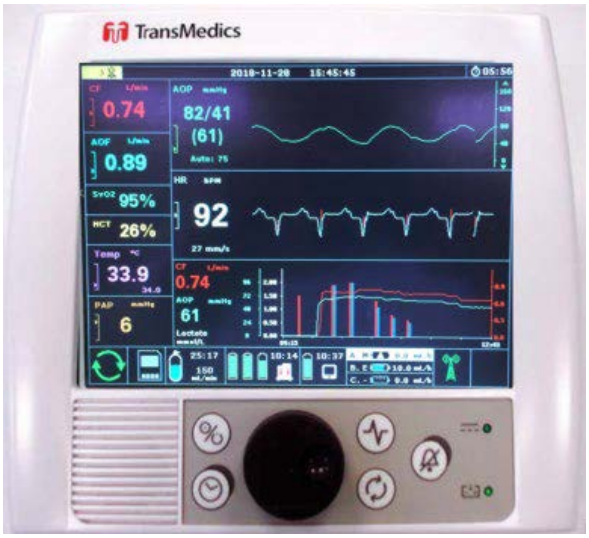
Cardioplegia is administered to the donor heart according to the institution's standard procedure, and the surgeon removes the heart in a standard fashion. Cannulae are then inserted retrograde into the aorta and pulmonary artery and secured appropriately, thus connecting the donor heart to the closed, extracorporeal HPM fluid circuit. The superior vena cava is tied off, and the inferior vena cava is left open as a vent until the heart is reanimated (regains beating state), at which point it is tied off. A left

ventricle vent is placed to assist with de-airing and to prevent distension. The temperature of the heart is gradually warmed to 34°C as the heart is perfused with the warmed, oxygenated blood that has been already supplemented with OCS Priming Solution. Cardiac rhythm is initiated by external defibrillation, if needed.

Maintenance of Donor Heart

The OCS Heart is intended to perfuse and maintain the donor heart during transportation to the recipient site. Pump flow and solution infusion rates are set to optimize coronary flow (CF), aortic pressure (AOP), and heart rate. Once initial perfusion parameters (e.g., AOP, CF), baseline lactate measurements, and stable heart rate are achieved on the OCS Heart (approximately within 30-45 mins), the heart is ready for transport. Lactate trend values are monitored throughout transport to assess perfusion of the donor heart, and adjustments in AOP and CF are made as needed. The Wireless Monitor displays parameters including heart rate, pump flow rate, coronary flow rate, aortic pressure, temperature, oxygen saturation, and hematocrit (HCT) levels. An off-the-shelf portable blood gas analyzer is utilized to check blood chemistry and lactate.

Figure 3: OCS Heart Wireless Monitor Display



During transport, the heart is maintained at a temperature of 34°C to minimize the metabolic demand by the heart and to meet the following target preservation parameters:

- Mean coronary flow range of 400-900 mL/min
- Mean aortic pressure range of 40-100 mmHg
- Mean heart rate range of 50-100 BPM
- Stable or declining arterial lactate.

Arresting the Donor Heart and Removal from the OCS Heart System

In accordance with the clinical study protocol, the donor heart is assessed at the recipient site. If the donor heart is deemed acceptable for transplantation (see Final Donor Heart Assessment Criteria below), the donor heart is cooled on the system by connection to a standard heater-cooler device and then arrested by administering a cold cardioplegia solution through the aortic access port of the HPM. After arrest is achieved, the OCS pump is turned off and supplemental topical cooling may be applied. The mechanical cooling, cold cardioplegia, and topical cooling are meant to ensure adequate myocardial protection during the period of removal from the OCS Heart to implantation of the donor heart. The donor heart is removed from the OCS Heart and placed in a sterile bowl filled with cold saline. The surgeon removes the OCS cannulae and prepares the donor heart for transplantation in accordance with standard surgical procedures.

Final Donor Heart Assessment Criteria

Accept for Transplantation

Donor hearts preserved on the OCS Heart System maintained within the following parameters:

- Total OCS™ arterial Lactate level < 5 mmol/L
- Stability of OCS™ Heart Perfusion Parameters within ranges:
    - CF 400-900 ml/min
    - AOP 40-100 mmHg

  LVH hearts may require higher CF and/or AOP

Reject for Transplantation

- Total OCS Heart System arterial lactate level >5 mmol/L at the end of OCS Heart System perfusion period
- Transplanting surgeon/heart failure cardiologist is clinically unsatisfied with donor heart evaluation after perfusion on the OCS Heart System.

Panel: As described in the clinical and pathology sections of this Summary, the Panel will be asked to comment on clinical concerns related to the potential for myocardial injury associated with the use of the OCS Heart System, as well as rejecting of donor hearts based on information derived from the OCS Heart System.

5. Regulatory History

Prior to submitting the current PMA for the OCS Heart (b)(4)), TransMedics submitted several other applications to FDA, including investigational device exemptions (IDEs), a prior PMA (b)(4) , and pre-submissions (Q-SUBs). **Table 1** shows the applications submitted to FDA that are directly related

to the OCS Heart System and the clinical data we will be discussing *(note: G180272 is ongoing, and data from this study are not included in our review of the current PMA)*:

Table 1: FDA Submissions related to the OCS Heart System

FDA Application	Application Content	Overview
G060127	**PROCEED II Study** – (b)(4) ; 128 subjects	International randomized, controlled clinical study comparing the safety and effectiveness of the use of standard donor heart preservation techniques to the use of the OCS Heart System to preserve donor hearts in a near-physiologic and beating state.
(b)(4)	Premarket Application (PMA) – analyses of clinical data obtained from G060127.	- PROCEED II met the Primary Study Endpoint (Effectiveness) of 30-day patient survival without mechanical circulatory support (non-inferiority test, non-inferiority margin of 10%). - PROCEED II demonstrated non-inferiority for the secondary safety endpoint of cardiac graft-related serious adverse events. However this composite endpoint was modified by the sponsor post-hoc, such that the original pre-specified safety endpoint was never analyzed. - The survival rate of patients with OCS Heart-preserved hearts was lower than that of control arm patients at all time points out to 5 years. - (b)(4) (b)(4)
G140111	EXPAND Clinical Study – (b)(4) 75 subjects	US single-arm study evaluating the use of the OCS Heart System, using near-physiologic, and beating state preservation, to maintain and perfuse donor hearts that may not meet current standard donor heart acceptance criteria for transplantation to potentially improve donor heart utilization. The data from this study was originally intended to supplement an approved OCS Heart System for Standard Hearts (b)(4) to broaden the indications for use.
(b)(4)	(b)(4)	
G140111/S029	EXPAND Continued Access Protocol (CAP) – (b)(4) ; 18 subjects and incrementally expanded to 75 subjects (b)(4)	Single-arm study to permit access to the device at EXPAND sites while the PMA was under review.
(b)(4)	Subject of current PMA - analyses of clinical data obtained from G140111 and G060127	
G180272	*DCD Heart Study - (b)(4) 9 for 212 subjects*	*Concurrently controlled IDE study of the use of the OCS Heart device for heart donation after circulatory death (DCD). Study ongoing.*
G180272/S011	*DCD Continued Access Protocol (CAP) (b)(4) for 90 subjects*	*Single arm study to permit access to the device during assembly and review of a PMA for DCD hearts*

5.1 EXPAND

Tables B.1 and B.2 in Appendix B provide a more detailed history of the major device design and clinical protocol changes over the course of the EXPAND clinical study. Below is a high-level summary:

- Full EXPAND IDE approval was granted on September 3, 2014
- First subject was transplanted with an OCS Heart System-supported heart on September 16, 2015
- Last subject was transplanted with an OCS Heart System-supported heart on March 25, 2018

OCS Heart System Design Changes

Several changes to the device design were made throughout the EXPAND study. For more details of the major changes made, please see Appendix B. In summary, major device modifications to the OCS Heart System during the EXPAND Study were made to mitigate problems with the AOP automatic mode and included removal of a compliance chamber and increases to the AOP and CF operating specifications. Prior to EXPAND Study enrollment, TransMedics changed the oxygenator and pump designs compared to the OCS Heart System used in PROCEED II.

Table 2 identifies key design differences between the OCS Heart System used in PROCEED II (final design used in G060127), EXPAND (original proposed design – G140111/Original) and EXPAND (final design changes made during G140111). There were subjects treated with each major design iteration within the EXPAND Study.

Table 2: Design and Use Differences for OCS Heart System Over Time

Design Features	PROCEED II (final design)	EXPAND (G140111/Original)	EXPAND (final design)
Novalung Oxygenator	X		
Maquet-i Small Adult Oxygenator		X	X
2nd compliance chamber		X	
One-way valve for 2nd compliance chamber		X	
Addition of "Y" prime line with pressure relief valve in perfusion module.		X	X
Cardinal Health MedSystem III pump	X		
SDS		X	X
AOP range 40-80	X	X	
AOP range 40-100			X
CF range 400-800	X	X	
CF range 400-900			X
Manual AOP*	X	X	X
Automatic AOP mode*		X	X

*AOP mode: adjustment of maintenance solution flowrate either automatically (automatic AOP) or Manually (manual AOP). Operator chooses AOP mode.

Clinical Protocol Changes

Several changes to the clinical protocol were made throughout the EXPAND study. For more details of the protocol changes made, please see Appendix B. In summary, some of the major protocol changes included a requested enrollment increase from 55 to 75 subjects after 87% of the subjects had already been enrolled (>90% of these subjects already had 30-day endpoint data available), and at the same time, a revised protocol (Version 1.4) included changes made to the statistical plan and study definitions.

Table 3: Number of Subjects Enrolled under TransMedics' Protocols

Protocol Version	Application/Supplement	Date	Subjects Enrolled (N)
Version 1.2	G140111/S001	October 8, 2014	23
Version 1.3	G140111/S015	July 18, 2016	35
Version 1.4	G140111/S018	August 10, 2017	17

EXPAND Study Design Considerations (SDC)

In 2012, Congress revised Section 520(g) of the Food Drug and Cosmetic Act such that,

> "*FDA will not disapprove an IDE because the investigational plan for a pivotal study may not support approval or clearance of a marketing application. However, if FDA believes modifications to the study are needed to achieve this objective, FDA will convey such considerations to the sponsor to provide greater clarity and predictability. In addition, FDA will convey to the sponsor considerations that FDA believes will be important for future submissions related to the proposed investigation.*"[1]

Any remaining clinical study design concerns are communicated to the sponsor of the IDE as "Study Design Considerations (SDC)" and "Future Concerns (FC),"[2] usually as an enclosure to the IDE letter. While FDA strongly recommends that the SDCs are addressed in a timely manner (to assure a dataset that will be acceptable to support a marketing application), revised Section 520(g) does not require the IDE sponsor to respond to the study design considerations, and the sponsor can complete their study without taking any of the study design considerations into consideration.

FDA provided 27 SDCs and 1 FC to the sponsor over the course of the TransMedics EXPAND IDE study (G140111) and 5 SDCs and 2 FCs related to the EXPAND CAP Protocol. Many of the SDCs forwarded to TransMedics were related to study design changes that FDA believed were needed for the EXPAND study to support marketing approval. FDA's recommendations were intended to enhance the study's scientific soundness and validity. Some of the more critical SDCs outlined in letters to

[1] FDA Decisions for Investigational Device Exemption Clinical Investigations - Guidance for Sponsors, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff - Document issued on August 19, 2014.
[2] Any changes to the study design needed to protect study subjects will be communicated as deficiencies that may result in IDE disapproval (as discussed in section 6) and will not be communicated as study design considerations.

TransMedics, and which were not adequately addressed during the IDE phase of the EXPAND study, include:

- The need for a control arm for the EXPAND study;
- A pre-specified safety endpoint hypothesis test;
- A clinically robust primary effectiveness endpoint;
- Methods for minimizing potential study bias; and
- Definitions of analysis populations

A complete list of the remaining SDCs and FCs as presented in FDA's (b)(4) letter (G140111/S018) is provided in Appendix C. This list of study design considerations represents the remaining SDCs that FDA believes would have increased study and data quality and validity had these SDCs been implemented into the EXPAND investigational plan in a timely manner.

5.2 EXPAND CAP

The EXPAND CAP study was approved on February 7, 2019 for 18 initial subjects with an increased sample size during the PMA review to 75 subjects (approved on October 16, 2020). At the time of EXPAND CAP database lock on August 26, 2020, there were at least 30-day data available for 41 subjects transplanted with EXPAND CAP donor hearts and 4 additional donor hearts perfused on the OCS Heart but turned-down for transplant.

EXPAND vs. EXPAND CAP

A CAP study is intended to permit continued access to the device while a PMA is under review and to potentially provide adjunctive safety and effectiveness data. As such, the CAP device design, study design, and enrolling sites are intended to be an extension of the original study. While there were no major device or study design changes made during the EXPAND CAP study, there were some subtle differences in the inclusion/exclusion criteria and analysis populations. Additionally, EXPAND CAP sites differed from the EXPAND sites. As will be discussed in more detail in Section 7.3:

- Only 3 of the10 EXPAND CAP sites also enrolled in EXPAND;
- (b) (6) contributed a majority of the patients to both EXPAND (39%) and EXPAND CAP (59%) enrollment; and
- EXPAND sites selected to participate in EXPAND CAP were known to have higher patient survival rates and donor heart utilization rates (92% and 81%, respectively) than the EXPAND sites that did not participate in EXPAND CAP (56% and 73%, respectively).

Other differences noted between the EXPAND and EXPAND CAP studies included the overall health/condition of the accepted donor hearts and of the intended recipients (e.g., EXPAND Status 1a/1b recipients totaled 99% of the enrolled population; EXPAND CAP Status 1-3 recipients totaled 61% of the enrolled population) – see Section 7.3.

FDA Comment: Enrollment of a majority of subjects at a single site (b) (6) selection of high performing sites, and overall condition of the donor hearts and recipients may have influenced outcomes in this EXPAND CAP study cohort.

EXPAND CAP Study Design Considerations

As indicated in Section 5.1 (and outlined in Appendix C), there were many outstanding Study Design Considerations (SDCs) that FDA conveyed throughout the course of the study and were intended to enhance the study's scientific soundness and validity. Although TransMedics provided justification for not adopting many of FDA's SDCs, FDA continues to believe that the incorporation of the recommended SDCs into the EXPAND and EXPAND CAP investigational plans would have increased study quality and validity.

6. Non-Clinical Testing

In Vitro/Bench Testing

The applicable in-vitro testing has been performed, and results were acceptable. Testing included electrical safety testing, electromagnetic compatibility, battery testing, sterility, packaging, packaging integrity testing, shelf life testing, biocompatibility, and performance testing on the OCS Heart System, the OCS Heart Console, and the Heart Perfusion Set (HPM plus HPS Accessories). Major changes made during the study were evaluated by risk analyses, and relevant testing was performed. For more details on the in-vitro testing and changes made throughout the study, please see Appendix D.

In Vivo Animal Studies

In (b)(4), TransMedics provided FDA with limited information from a non-controlled, non-GLP animal study on N=2 *ex vivo* porcine hearts. These hearts were preserved on the OCS Heart System for 6 hours and transported in an SUV automobile for at least 30 minutes during preservation. Target Aortic Pressure (AOP) was 40-100 mmHg and target Coronary Flow (CF) was 400-900 ml/min, which are the recommended operating specifications for the OCS Heart System (G140111/S015).

Physiologic parameters (e.g., AOP, CF, temperature, heart rate, HCT, lactate) were monitored. However, histologic evaluation of the two hearts or other assessments of tissue viability or injury (e.g., ATP content, troponin) was not provided. In addition, there were no control hearts treated with the current standard of care (cold static preservation).

Pre- and post-preservation heart weights indicated a weight gain of 74.1 g (22%) and 69.7 g (20%) in the two perfused animal hearts following 6 hours of OCS Heart System perfusion (Table 4).

Table 4: Animal Heart Pre-, Post-perfusion Weight (N=2)

Animal Heart	Pre-perfusion Weight (g)	Post-perfusion Weight (g)
Heart #1	343.3	417.4
Heart #2	357.2	426.9

Increased tissue weight following OCS Heart System perfusion raises concerns for changes in cellular structure, functionality, and tissue health. This weight gain may be secondary to organ edema and raises concerns for myocardial injury that could negatively impact organ viability and functionality post-transplant.

Accordingly, FDA believes that the animal testing completed and submitted to FDA leaves several important questions of safety and performance unanswered for the current PMA.

Previously, TransMedics provided four non-GLP porcine studies (N=2 or 3 animals each) in (b)(4) and G140111/S013 (see Appendix D, Table D.10 for more information on these studies). Testing objectives largely centered on validating design changes as the device was modified. The sponsor did not perform comprehensive animal studies that evaluated the final device design in a clinically relevant setting. Important insights into device performance and safety and effectiveness could have been addressed by well-designed and conducted animal studies. Important limitations of the animal testing include:

- Translatability of data to support safety and effectiveness of the subject device is dependent on pre-clinical testing evaluating the final or near-final device. Animal testing evaluated earlier device versions and was relied on as part of the OCS Heart System verification and validation. This results in limitations of the animal studies with respect to device performance and safety.
- The animal study sample sizes were small.
- Animal testing was conducted without controls, so data interpretation are challenging when comparing safety and effectiveness to cold storage, the current standard of care. This may be especially important since no in vivo studies evaluating organ viability were submitted or completed prior to human use.
- Animal testing did not evaluate myocardial histology following perfusion with the OCS Heart device. Histology provides valuable information relevant to device safety and effectiveness that cannot be readily obtained from human clinical studies. (Note: The sponsor identifies a study presented at ISHLT by Dr. Padera, et al, 2009 [Pathology Influences Device Development: The TransMedics Organ Care System for Heart. The Journal of Heart and Lung Transplantation; February 2009], where it was stated that histology was performed. However it should be noted that this study was presented to FDA as an abstract, was performed to "optimize device development", and full study materials (including the final study protocol, test methods, and complete original histologic results) were not provided to FDA for us to confirm study findings and evaluate their relevance to the OCS Heart System used in the EXPAND Study.)

- Animal studies were non-GLP despite numerous requests for GLP compliance and were conducted without a GLP certified quality assurance unit. The sponsor noted the cost prohibitive-nature of a quality assurance unit as justification for animal studies not being in compliance with GLP recommendations.

FDA Comment: Perfusion with the OCS Heart System is intended to assess and preserve tissue viability and reduce myocardial injury in donor hearts. Well-designed and executed animal studies evaluating hearts supported with the OCS Heart System compared to standard of care static cold storage hearts could provide valuable insights into myocardial preservation and injury patterns between these two strategies. For the present PMA, animal studies were limited in scope and number, and importantly, did not include myocardial histologic analyses.

7. Clinical Studies

This clinical review summarizes the PMA submission from TransMedics for its OCS Heart System. FDA presents the trial design, information on the execution of the study, statistical cohorts, and analyses followed by what FDA believes is the most informative analyses to assess the safety and effectiveness of the OCS Heart System. FDA includes comments in each section to point out concepts and information that FDA believes are of key contextual importance when evaluating study results.

Unlike the established approach of donor heart preservation in a cold, static condition after crystalloid-based cardioplegia, the OCS Heart maintains a donor heart in a blood-perfused, near-normothermic, beating state. TransMedics suggests that preserving a donor organ with its device:

- optimizes oxygen and substrate delivery, while also replenishing nutrients that are depleted due to the brain-dead condition in the body of the donor;
- allows for resuscitation of the donor heart into a beating physiologic state *ex-vivo*, thereby enabling assessment of the donor heart's viability;
- reduces time-dependent ischemic injury to the donor heart during preservation, thus eliminating existing logistical and geographical barriers to heart transplantation; and
- allows physicians to judge with lactate levels a donor heart's condition and suitability for transplantation, thus minimizing the risk of transplanting poorly functioning hearts.

In January 2006, TransMedics initiated its first feasibility clinical trial of the device (PROTECT) in Europe with 20 patients; 15 additional European patients were enrolled into the similar PROTECT II post-marketing study after the device's September 2006 EU marketing approval. IDE G060127 began in 2006 with a US-based pilot study (the PROCEED trial, which FDA initially approved for 5 subjects) that ultimately enrolled 15 allograft recipients at 4 centers between April 2007, and July 2008. All three of these initial clinical protocols followed patients for 30 days post-transplantation, and the primary endpoint in each was 7-day patient survival.

The results of these small pilot trials informed the design of the follow-on US pivotal study, PROCEED II, which was fully approved by FDA in its fourth iteration (version 1.3) in July 2008. The final protocol (version 1.6) was to enroll 128 patients ("recipients," not donor allografts) with 1:1 randomization of the donor allografts to either standard cold preservation storage and transport or OCS Heart perfusion and transport. In December 2014, TransMedics submitted PMA (b)(4) to FDA, seeking marketing approval for use of the device with standard criteria donor hearts. (b)(4) relied almost exclusively upon the clinical results from PROCEED II.

FDA performed a detailed and complete review of (b)(4), leading to several major concerns about PROCEED II's clinical results and the device's safety and effectiveness profile when used with standard criteria donor hearts. TransMedics subsequently withdrew the PMA. The OCS Heart has not been approved by FDA in any population for any indication for use.

The current PMA, (b)(4), concerns donor hearts having one or more characteristics that render them "extended" or "expanded-criteria" cardiac allografts as defined by the protocol, as opposed to "standard" donor organs. In June 2014, with knowledge of the PROCEED II results, the sponsor submitted a separate IDE (G140111) to specifically evaluate the OCS Heart System when transporting extended-criteria donor hearts in the single-arm EXPAND Heart ("EXPAND") study. At the time of FDA approval of EXPAND's protocol (September 2014), the PROCEED II clinical study report had not yet been submitted to FDA for review. FDA's approval of EXPAND included multiple study design considerations and recommendations about trial design (see Appendix C Study Design Considerations), including concerns that the trial lacked a comparator control group.

FDA recognizes that it can be difficult to fully characterize the "standard-ness" of a donor heart, particularly in situations where the distinction between standard- and extended-criteria depends substantially upon a clinician's *a priori* estimate of required preservation time. FDA also believes that PROCEED II is relevant for any evaluation of the EXPAND study because there is overlap between the two studies' donor heart populations and PROCEED II was a randomized study with more extensive longer-term follow-up available. FDA communicated to the sponsor since 2014 that interpretation of the EXPAND trial would be framed by inferences drawn from the randomized PROCEED II trial.

Table 5: Clinical Investigations with the OCS Heart System

Study	Location	Years	Subjects Enrolled	Study Design	Donor Heart
PROTECT	EU	2006-7	25	Single-arm	Standard-criteria
PROTECT II Registry	EU	2007-8	20+	Registry	Standard-criteria
PROCEED	US	2007-8	16	Single-arm	Standard-criteria
PROCEED II (G060127 (b)(4)	**US and EU**	**2009-13**	**128**	**Randomized Controlled**	**Standard-criteria**

EXPAND (G140111(b)(4)	**US**	**2015-18**	**96 (*CAP 41*)**	**Single-arm**	**Extended-Criteria**
OCS Heart U.S. DCD Heart Trial (G180272)	US	2019 - present	162 (*CAP ongoing*)	Concurrent Control	Donation after circulatory death (DCD)

7.1 PROCEED II (G060127)

7.1.1 Study Objective

The OCS Heart's hypothetical premise is that appropriately controlled warm-blood-based perfusion during organ storage and transport yields a better-functioning allograft after transplantation compared to standard-of-care cold static preservation. The clinician can modulate device pump flow and solution infusion rates in an effort to optimize coronary flow, aortic pressure, and heart rate. The rationale for a trial was to investigate the OCS Heart's ability to:

> "…improve organ preservation and overcome the limitations of current organ preservation techniques, such as time-dependent ischemia and reperfusion injuries…thereby facilitating an optimal donor/recipient matching process and geographical distribution of organs."

To that end, the primary objective of PROCEED II was "to compare the safety and effectiveness of the OCS Heart System with the existing cold static cardioplegia standard of care for the preservation of donor hearts."

FDA agreed with the rationale for the PROCEED II IDE trial, given experience with cardiopulmonary bypass (CPB) and extracorporeal membrane oxygenation (ECMO) and the known limitations of cold static preservation techniques. An implicit objective of the OCS Heart is to increase organ preservation time flexibility. PROCEED II was not, however, prospectively designed to evaluate the interaction of transport (preservation) time with safety and effectiveness endpoints. In PROCEED II, despite 1:1 randomization prior to donor in-chest evaluation, donor hearts transported with the OCS Heart had substantially longer preservation times than control arm donor hearts preserved with cold, static preservation solution (the current standard of care, SOC). In EXPAND and EXPAND CAP, as discussed later, the most frequent characteristic qualifying a donor heart for inclusion as extended-criteria organ was the expectation by transplanting clinicians of prolonged (≥ 4 hours) ischemic time if cold static preservation had been utilized.

7.1.2 Study Design

PROCEED II was a multi-center randomized controlled trial designed to allocate 128 enrolled recipient patients randomized (1:1) to OCS Heart- (treatment arm) or SOC-preserved (control arm) donor hearts.

Inclusion and Exclusion Criteria

Separate inclusion and exclusion criteria were used for prospective donor organs and consented recipients.

Recipient Eligibility Criteria

Recipients were screened for eligibility on two occasions (at the time of consent and again on the day of planned transplantation).

Inclusion

- Registered male or female primary heart transplant candidate
- ≥ 18 years old
- Signed, written informed consent document and authorization to use and disclose protected health information

Exclusion

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

*During the course of the trial, sternotomy and concurrent transplant exclusion criteria were changed. The original criteria excluded patients with > 2 previous sternotomies and concurrent kidney transplant. Two OCS Heart-randomized patients remained screen failures by the sponsor on the basis of the original exclusion criteria.

Donor Heart Eligibility Criteria

Inclusion

- < 60 years old
- Mean arterial blood pressure > 60 mm Hg at the time of final heart assessment
- Satisfactory echocardiography assessment defined as:
  - Ejection fraction > 40%
  - Absence of severe segmental wall motion abnormalities
  - Absence of left ventricular hypertrophy (interventricular septum (IVS) and posterior wall thickness (PWT) < 1.3 cm)
  - Absence of valve abnormalities (trace to mild valvular regurgitation acceptable)

Exclusion

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

- Dobutamine > 10 μg/kg/min
- Milrinone > 0.3 μg/kg/min
- Epinephrine > 0.03 μg/kg/min
- Norepinephrine > 0.03 μg/kg/min
- Any bolus dose of the above vasoactive agents prior to explants that would result in exceeding the above stated criteria
- Presence of any exclusion criterion based on the standard practice of the investigational site

FDA Comment: PROCEED II did not have an inclusion criterion based upon expected cross-clamp time, and those data were not captured. All donor organs in EXPAND had to meet a criterion of an expected cross-clamp time (i.e., anticipated ischemic time if transported without using the OCS Heart) ≥ 2 hours.

ENDPOINTS

PROCEED II had four powered endpoints, each of which tested a non-inferiority hypothesis.

Primary Study Endpoint (Effectiveness)

The Primary Study Endpoint evaluated effectiveness, defined as patient survival at post-operative day (POD) 30 following transplantation with the originally transplanted heart and without any mechanical circulatory support (MCS) device:

$$H_O: \pi OCS < \pi SOC - \delta$$
$$H_1: \pi OCS \geq \pi SOC - \delta$$
$$\delta = 0.10$$

where δ is the non-inferiority margin, and πOCS and πSOC are the respective proportions of subjects surviving at POD 30:

- with the originally transplanted heart; and
- without a mechanical circulatory assist device on POD 30.

If non-inferiority was demonstrated, the protocol allowed for superiority testing.

Because the MCS endpoint criterion was limited to MCS use *on day 30*, it excluded temporary MCS use for severe allograft dysfunction that was subsequently discontinued prior to POD 30.

At the time of IDE approval, FDA acknowledged the sponsor's position that effectiveness results beyond 30 days would likely be influenced by many factors other than the allograft preservation technique. However, the Agency also maintained that the randomized nature of PROCEED II would mitigate much of the potential confounding. FDA accepted the endpoint's 30-day time frame, but repeatedly stressed--beginning with the IDE's feasibility phase approval in 2006--the importance of longer-term follow-up data regarding effectiveness (patient survival and graft survival) and safety (serious adverse events). The sponsor did not prospectively collect outcome data beyond 30 days, and FDA requested *post hoc* survival analyses based

upon data from the Scientific Registry of Transplant Recipients (SRTR), a mature transplantation registry funded and overseen by the US Health Resources and Services Administration (HRSA). Longer-term survival data for non-US (OUS) recipients were separately collected *post hoc* by the sponsor.

FDA Comment: Although *post hoc* in nature, FDA believes the longer-term survival analyses for OCS Heart and SOC patients are essential components of the OCS Heart's safety and effectiveness assessment.

Secondary Endpoint (Safety)

There was a single pre-specified safety endpoint, the incidence of Clinical Events Committee (CEC)-adjudicated cardiac-related serious adverse events (SAEs) up to 30 days following transplantation:

$$H_O: \tau OCS > \tau SOC + \delta$$
$$H_1: \tau OCS \leq \tau SOC + \delta$$
$$\delta = 0.10$$

where τOCS and τSOC are the respective proportions of patients experiencing at least one cardiac-related SAE, and δ is the non-inferiority margin.

The approved IDE protocol pre-specified 11 cardiac-related SAEs as components of the composite safety endpoint (Table 6).

Table 6: PROCEED II Safety Endpoint Serious Adverse Event Definitions

AE Team	Definition for Serious*	Cardiac Related
Acute Rejection	An endomyocardial biopsy finding of ISHLT 3R or higher grading	Yes
Balloon pump (IABP)	Any use of an aortic balloon pump required to correct arrhythmia post-transplant for greater than eight (8) hours. The use of an IABP for less than 8 hours is anticipated as standard practice in some institutions.	Yes
Cardiac Arrhythmia	Any documented arrhythmia that results in clinical compromise (e.g., oliguria, presyncope, or syncope, tachycardia, bradycardia) that requires hospitalization or occurs during the hospital stay post transplant. Cardiac arrhythmias are classified as 1 or 2 types: 1.) Sustained ventricular arrhythmia requiring defibrillation or cardioversion 2.) Sustained supraventricular arrhythmia requiring drug treatment or cardioversion	Yes
Cardiogenic Shock	Decreased cardiac output and evidence of tissue hypoxia SvO2 < 50% or lactic acidosis) in the presence of adequate intravascular volume. Specifically, the hemodynamic criteria for cardiogenic shock are: 1.) Sustained hypotension (systolic blood pressure <80 mmHg for at least 60 min) and 2.) A reduced cardiac index (<2.0 L/min/m2) in the presence of elevated pulmonary capillary occlusion pressure (>18 mmHg). 3.) Also any newly installed Intra aortic balloon pump to come off bypass.	Yes
Graft Failure	Primary or nonspecific severe acute heart dysfunction necessitating the sustained use of a mechanical support device (VAD or ECMO), listing for transplant or re-transplant.	Yes
Heart Failure	Right Heart Failure: Symptoms and signs of persistent right ventricular dysfunction [central venous pressure (CVP) > 18 mmHg with a cardiac index <2.0 L/min/m2 in the absence of elevated left atrial /pulmonary capillary wedge pressure (greater than 18 mmHg), tamponade, ventricular arrhythmias or pneumothorax] requiring either RVAD implantation or inotropic therapy beyond 7 days or what is typical for inotropic management at the site. Left Heart Failure: Symptoms and signs of persistent left ventricular dysfunction (left-atrial pressure > 18 mmHg with a cardiac index <2.0 L/min/m2) in the absence of hemo-pericardium, pneumo-pericardium, hemothorax or pneumothorax, requiring either LVAD implantation or Inotropic therapy, 7 days or more after transplant.	Yes
Hypertension	New onset blood pressure elevation greater than or equal to 140mmHg systolic or 90 mmHg diastolic	Yes
Hypotension	Systolic less than 90 mmHg or diastolic less than mmHg leading to fainting	Yes
Myocardial Infarction	Peri-Operative Myocardial Infarction: The clinical suspicion of myocardial infarction together with CK-MB or Troponin > 10 times the local hospital upper limits or normal, found within 7 days following transplant together with ECG and/or echo cardiogram findings consistent with acute myocardial infarction. Non-Perioperative Myocardial Infarction: The presence at > 7 days post-transplant of the following criteria: 1.) ECG with a pattern or changes consistent with myocardial infarction; and 2.) Troponin or CK (measured by standard clinical pathology/laboratory medicine methods) greater than the normal range for the local hospital with positive MB fraction (≥ 3% total CK). This should be accompanied by a new regional LV or RV wall motion abnormality on a myocardial imaging study.	Yes
Pericardial Effusion	Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade and those without signs of tamponade.	Yes
Valve Disease	Any disease process (e.g.: insufficiency or stenosis) involving one or more of valves of the heart (mitral, aortic, pulmonary and tricuspid). The disease will be considered serious if the valvular abnormality was diagnosed as moderate to severe in an echo reading.	Yes

However, the secondary safety endpoint analysis presented by the sponsor in (b)(4) only incorporated 3 of the original SAE components:

- graft failure requiring MCS or listing for re-transplantation;
- left- or right-sided heart failure;
- myocardial infarction or moderate/severe mitral regurgitation.

The sponsor noted that the change to the definition of the safety endpoint's components was approved by the PROCEED II Steering Committee and the CEC on or about 2012 (trial enrollment had begun in 2009). The sponsor maintained that the change ensured "adverse events that [comprised] the endpoint of Cardiac (Graft-Related) Serious Adverse Events were directly related to the function of the transplanted donor heart (graft) to support the circulatory needs of the recipient." FDA was not aware of this protocol change, and the *post hoc* modification to the analysis plan was never approved by FDA. Several clinically important SAEs such as acute rejection, cardiac arrhythmia, and pericardial effusion occurred in study subjects but were not captured in the PMA's safety endpoint analysis.

FDA Comment: FDA disagrees with the sponsor's claim that the intent of the safety endpoint was limited to capturing SAEs "directly related to the function of the transplanted donor heart (graft) to support the circulatory needs of the recipient." FDA believes that the pre-specified safety endpoint was appropriate for the objective of PROCEED II, and that the limited sponsor-reported safety analysis was sub-optimal.

Secondary Endpoints (Effectiveness)

There were two non-hierarchical secondary effectiveness endpoints: (1) the incidence of rejection and (2) the length of Intensive Care Unit (ICU) admission.

Rejection endpoint

The first secondary effectiveness endpoint compared rejection episodes by POD 30:

$$H_O: \tau OCS > \tau SOC + \delta$$
$$H_1: \tau OCS \leq \tau SOC + \delta$$
$$\delta = 0.10$$

where δ is the non-inferiority margin, and τOCS and τSOC are the respective proportions of subjects exhibiting rejection by POD 30 defined as:

- International Society for Heart & Lung Transplantation (ISHLT) grade 2R (moderate) or 3R (severe) acute rejection on any surveillance endomyocardial biopsy (core laboratory reading); or
- clinically symptomatic rejection requiring augmentation of immunosuppressive therapy.

There was no pre-specified imputation plan for missing endomyocardial biopsy data. The sponsor substituted site biopsy readings for missing core laboratory biopsy readings.

ICU Stay endpoint

The second secondary effectiveness endpoint compared length of post-transplantation initial ICU stay:

$$H_O: \lambda OCS > \lambda SOC + \delta$$
$$H_1: \lambda OCS \leq \lambda SOC + \delta$$
$$\delta = 12 \text{ hours}$$

where λOCS and λSOC are the respective median lengths of ICU stay after transplantation, and δ is the non-inferiority margin.

Exploratory Endpoints

The protocol did not pre-specify exploratory endpoints, subgroup analyses, or sensitivity analyses.

FDA requested the following *post hoc* endpoint and subgroup analyses:

- Longer-term survival (Kaplan-Meier analysis)
- Primary Study Endpoint tipping point analysis
- Primary Study Endpoint, preservation-time stratification
  - ≤ 4 hours
  - > 4 hours
- Primary Study Endpoint analysis adjusted for the following baseline covariates:
  - Pre-operative MCS use
  - Cardioplegia solution use

ANALYSIS POPULATIONS

Enrollment into PROCEED II followed a pre-specified process. Recipient consent was obtained at screening, the time of initial comparison to the pre-specified inclusion and exclusion criteria. A second assessment of recipient eligibility based upon inclusion/exclusion criteria (i.e., a second screening of consented recipients) took place at the time a potential donor heart meeting inclusion/exclusion criteria was identified. At this point, the consented recipient was randomized to OCS Heart or SOC. Once the study site's organ procurement team confirmed donor heart eligibility with an in-chest evaluation, the recipient patient was considered enrolled. Per the protocol:

> "Potential subjects who are initially consented and screened but are found to be ineligible for enrollment as part of final eligibility evaluations; and, subjects who are eligible based on the first and second evaluations but for whom it is determined at the donor site that no matching or eligible donor is found, will not be considered enrolled or part of the "intent to treat" population."
>
> "A screen failure is a potential subject from whom an informed consent is obtained but in whom treatment within the context of the investigation is not attempted because it is determined that the subject does not meet all of the eligibility criteria during the second evaluation."

Recipient Populations

- Safety population: All subjects who receive a heart transported by either OCS Heart or SOC. If the heart is transported partially using the OCS Heart and partially using SOC, the analysis is per the initial treatment.

  The Safety population was specified as the primary analysis population for the secondary safety endpoint.

- Intention-to-Treat (ITT) population: All randomized subjects for whom it is determined at the donor site that there is a matching and eligible heart.

  ITT was specified as a supplemental analysis for the Primary Study Endpoint.

FDA Comment: FDA generally considers patient enrollment to take place when signing the informed consent form, thereby defining an unbiased intention-to-treat (ITT) population from which daughter analysis populations are derived. Although FDA acknowledged PROCEED II's logistical justifications for randomization prior to definitive enrollment, this process may have caused a selection bias. This issue was discussed with the sponsor. FDA believes the protocol-defined ITT population in PROCEED II is more accurately considered a "modified" ITT (mITT) population.

- Per Protocol (PP) population: All randomized subjects who are transplanted and have none of the following major protocol violations:
  - Ineligible for study per recipient inclusion/exclusion criteria
  - Ineligible for study per donor heart inclusion/exclusion criteria

  PP was specified as the primary analysis for the Primary Study Endpoint.

  Five OCS Heart-randomized donor hearts (7%) for four patients were turned down and not transplanted by investigators after meeting eligibility, preservation, and transport (see Section 6.3 Turned-Down Hearts: Clinical and Clinicopathologic Analyses).

FDA Comment: FDA generally considers a Per Protocol population to include patients who adhere to protocol requirements without major violations. PROCEED II defined PP as transplanted recipient-donor heart matches that met all inclusion and exclusion criteria. The turn-down of OCS Heart donor organs after preservation functionally represented a secondary selection process not applied to SOC-randomized donor hearts. FDA believes the non-inferiority analyses based upon the PP population may therefore be biased in favor of the treatment arm.

- Treated (or As Treated, AT): All randomized subjects who receive a donor heart transported either by the OCS Heart System or the SOC subsequent to randomization. If the heart was transported partially using the OCS Heart and partially using SOC, analysis was per the initial treatment.

AT was specified as an analysis population for both secondary effectiveness endpoints and as a supplemental population for the Primary Study Endpoint.

- Completed Treatment (CT): All subjects in the treated population who complete the study. CT was specified as an analysis population for the ICU stay secondary effectiveness endpoint.

FDA Comment: FDA does not believe that the CT population analysis provides important information regarding OCS Heart performance in PROCEED II, since "completed treatment" was not defined in the study protocol, and it excluded patients who failed the Primary Study Endpoint due to death.

Donor Heart Populations

- OCS Heart Population: All hearts that were transported by the OCS Heart System. This cohort included the turned-down hearts mentioned above, but excluded any hearts:
  - for patients withdrawn/screen-failed after OCS Heart transport; or
  - instrumented for OCS Heart but converted to SOC prior to transport.

- Transplanted Donor Heart Population: All transplanted hearts that were transported as randomized. This donor heart population, analogous to a "Per Protocol" donor heart population, was not pre-specified.

7.1.3 Patient Accountability

Clinical Sites

The trial had 12 enrolling sites, 8 in the US, 2 in the UK and 1 each in Italy and France. Two of the 8 US sites did not transplant any enrolled subjects during the trial. Enrollment initiated on March 21, 2009, and the study was completed on October 17, 2013.

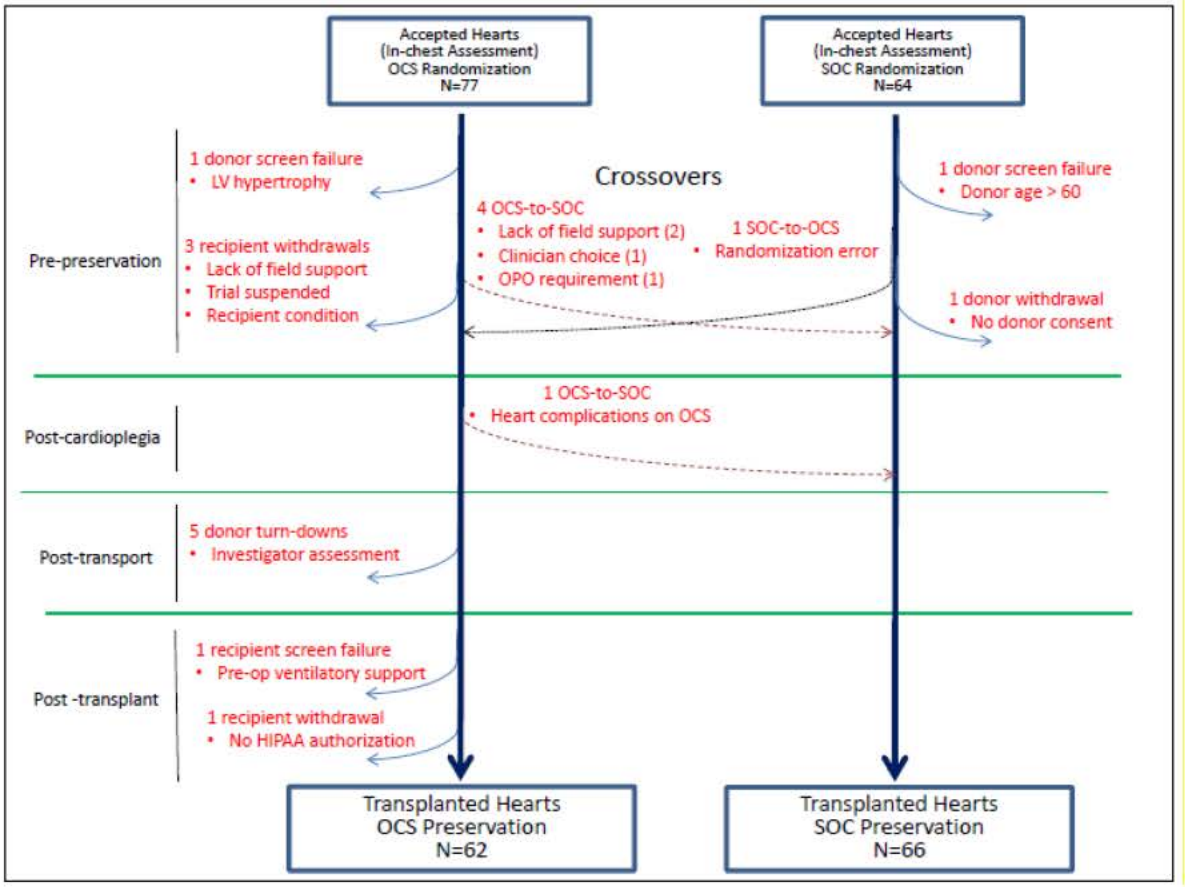
The protocol did not pre-specify an enrollment cap for individual sites, but FDA had requested that by the end of the study, no more than 20% of the total patients be enrolled at any one site. Two sites in Los Angeles, California (b) (6)) collectively contributed 57% of the study subjects (Table 7).

Table 7: PROCEED II Clinical Study Sites and Enrollment

Site Name	Country	SOC	OCS	# Randomized Patients
(b) (6)	USA	8	8	16
	USA	20	22	42
	USA	10	8	18
	USA	1	0	1
	USA	2	1	3
	USA	4	6	10
	FR	3	4	7
	USA	20	20	40
	UK	0	1	1
	UK	1	3	4
	IT	0	1	1
	USA	0	0	0
Total		69	74	143

Enrolled Donor Hearts

Figure 4: Donor Heart Allocation

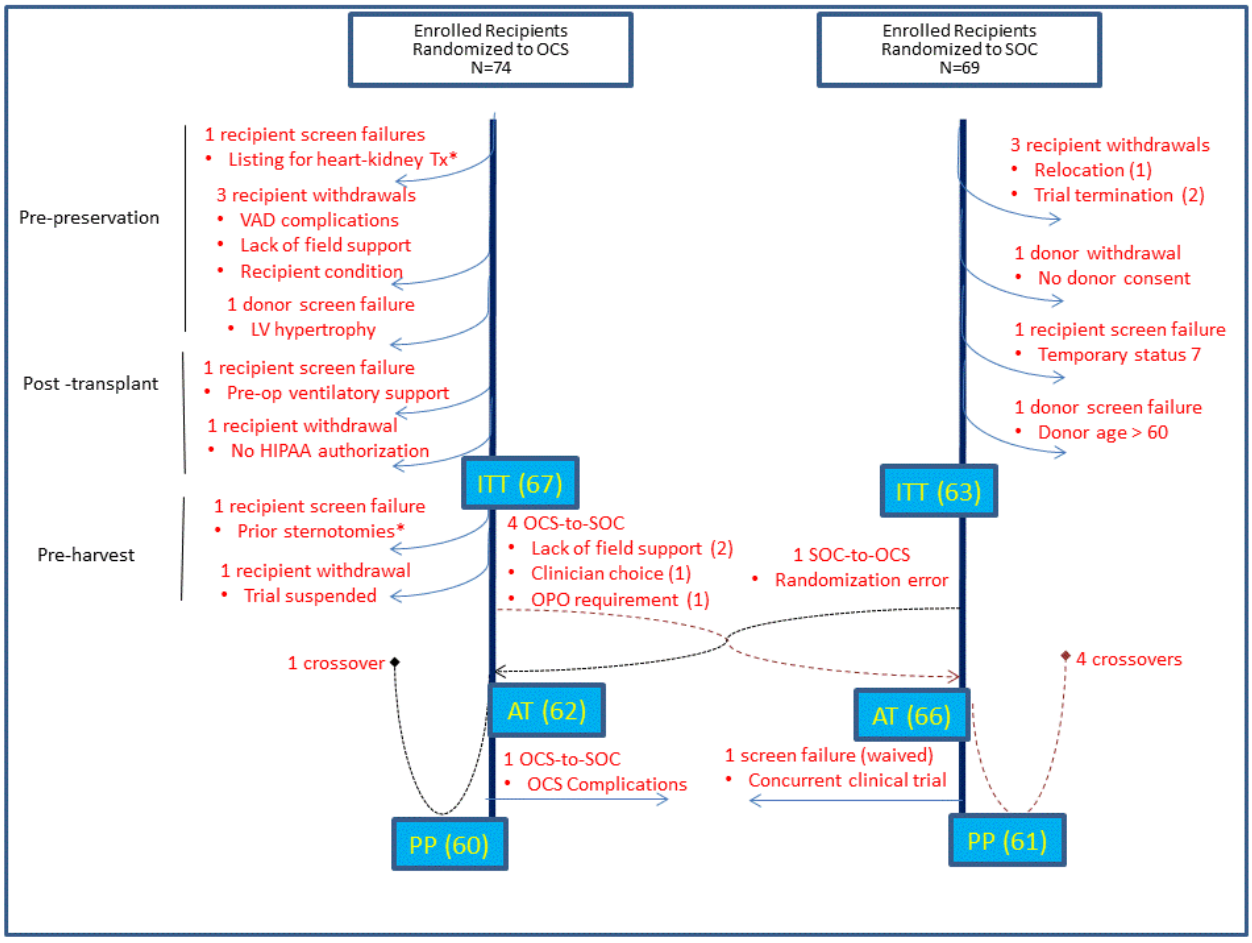


*Randomization occurred prior to enrollment.

OPO = Organ Procurement Organization

ENROLLED RECIPIENTS

Figure 5: Recipient Allocation



*Status 7 is UNOS terminology for "not active"

Among the accepted donor hearts:

- 6/77 (7.8%) OCS Heart-randomized and 2/64 (3.1%) SOC-randomized hearts were not included in the study on the basis of screening failures or patient withdrawal.
- 5/77 OCS Heart-randomized (6.5%) and 1/64 (1.6%) SOC-randomized hearts were involved in treatment crossovers.
- 5/77 OCS Heart-randomized (6.5%) hearts were deemed not suitable for transplantation after transport. These hearts were not included in any study endpoint analyses. See Section 6.3 Turned-Down Hearts: Clinical and Clinicopathologic Analyses for a discussion of hearts perfused on the OCS Heart device but turned down for transplantation.

Among the enrolled and randomized recipients:

- 14/74 (19%) OCS Heart-randomized and 8/69 (12%) SOC-randomized patients were not included in the PP Primary Study Endpoint analysis.
  - Two OCS Heart screen failures/withdrawals occurred post-transplantation.
  - Two screening failures (asterisks in diagram) were for exclusion criteria subsequently removed from the protocol.

FDA Comment: Post-randomization screen failures, withdrawals, and treatment crossovers were more common in OCS Heart-randomized subjects and donor hearts. FDA understands the complexities associated with organ procurement and transplantation. However, imbalances in rates of screen failures, withdrawals, and treatment crossovers raise concerns about unintended bias in favor of the OCS Heart group despite 1:1 randomization in PROCEED II.

7.1.4 Demographics and Characteristics

ITT Population Donor Heart Recipients

Key comparative baseline patient demographics and characteristics for the ITT population are shown in Table 8 (corresponding to Table 11-1 in the PROCEED II Clinical Study Report).

Table 8: Recipient Demographics and Baseline Characteristics for the ITT Population

Parameter	Statistic	OCS (N=67) n (%)	Control (N=63) n (%)	p-value [1]
Age (years)	N	67	63	
	Mean (SD)	53.09 (13.09)	54.46 (13.55)	0.5592
	Median	55.51	56.60	
	Min, Max	19.9, 74.9	20.4, 76.1	
Gender				0.0867
Male	n (%)	57 (85.1)	45 (71.4)	
Female	n (%)	10 (14.9)	18 (28.6)	
Race				0.8825
American Indian or Alaskan Native	n (%)	0 (0.0)	0 (0)	
Asian	n (%)	5 (7.8)	6 (9.8)	
Black of African American	n (%)	7 (10.9)	6 (9.8)	
Hispanic	n (%)	6 (9.4)	7 (11.5)	
Native Hawaiian or Other Pacific Islander	n (%)	1 (1.6)	1 (1.6)	
White	n (%)	41 (64.1)	40 (65.6)	

Other	n (%)	4 (6.3)	1 (1.6)	
Unknown	N	3	2	
Blood Type				0.4965
O	n (%)	32 (47.8)	22 (34.9)	
A	n (%)	22 (32.8)	27 (42.9)	
B	n (%)	7 (10.4)	8 (12.7)	
AB	n (%)	6 (9.0)	6 (9.5)	
PRA%	N	64	61	
	Mean (SD)	2.1 (6.9)	3.2 (7.5)	0.3932
	Median	0.0	0.0	
	Min, Max	0, 40	0, 38	

(1) p-value is based on the two-sample t-test for continuous variables and Fisher's Exact Test for categorical variables

Baseline clinical characteristics were generally similar between study groups, with the majority of subjects being white males. The SOC arm had a numerically higher proportion of women, and the OCS Heart arm had a numerically higher proportion of blood type O patients. Blood type O patients generally comprise a group of transplant candidates for whom waiting times can be prolonged (~50% of type O "universal donor" organs may go to non-Type O recipients). A similar proportion of patients had no prior sternotomy (~50%).

Day-of-transplantation MCS device use was present in 28% of OCS Heart and 33% of SOC subjects. More SOC patients were on intra-aortic balloon pump (IABP) support on the day of transplantation. IABP MCS is typically a shorter-term intervention used for acute hemodynamically unstable patients. In 2018, the Organ Procurement and Transplantation Network (OPTN) modified the US donor heart allocation system to assign higher medical urgency priority to candidates on an IABP (Status 2) vs. subjects with normally functioning durable VADs (Status 3 and 4). The use of MCS devices prior to transplantation is shown in Table 9.

Table 9: Mechanical Support on the Day of Transplant, ITT and Treated Populations

ITT Population			
Support	OCS (N=67) n/N (%)	Control (N=65) n/N (%)	p-value (1)
IABP	0/66 (0.0)	6/63 (9.5)	0.0119
VAD	19/66 (28.8)	15/63 (23.8)	0.5541
ECMO	0/62 (0.0)	0/63 (0.0)	--
Treated Population*			
Support	OCS (N=62) n/N (%)	Control (N=66) n/N (%)	p-value
IABP	0/62 (0.0)	6/66 (9.1)	0.0281
VAD	18/62 (29.0)	15/66 (22.7)	0.4276
ECMO	0/58 (0.0)	0/66 (0.0)	--
VAD duration (Days)			
Mean	350	481	0.198
Std Dev	229	321	
Median	409	581	
Min	23	56	
Max	704	1052	

(1) P-value is based on Fisher's Exact Test

* Treated Population is the same as "As Treated"

Donor Heart Populations

Key comparisons of the "Transplanted Donor Heart" populations and the broader "OCS Heart" population (which includes the five turned-down hearts) are shown in Table 10.

Table 10: Donor Organ Clinical and Demographics Characteristics

	Transplanted Donor Heart Population			OCS Heart Population
Parameter	OCS (N=61) n (%)	Control (N=62) n (%)	p-value	OCS (N=67) n (%)
Cause of Death			0.9874	
Anoxia	14 (23.0)	13 (21.0)		15 (22.4)
Cerebrovascular/Stroke	17 (27.9)	17 (27.4)		18 (26.9)
Head Trauma	26 (42.6)	28 (45.2)		29 (43.3)
CNS Tumor	0 (0.0)	1 (1.6)		0 (0.0)
Other	4 (6.6)	3 (4.8)		5 (7.5)
Chest Trauma			0.3955	
Yes	8 (13.1)	5 (8.1)		10 (14.9)
No	53 (86.9)	57 (91.9)		57 (85.1)
Hypotensive Episodes			0.5804	
Yes	22 (36.1)	26 (41.9)		24 (35.8)
No	39 (63.9)	36 (58.1)		43 (64.2)
Cardiac Arrest			0.8376	
Yes	16 (26.2)	15 (24.2)		18 (26.9)
No	45 (73.8)	47 (75.8)		49 (73.1)

	Transplanted Donor Heart Population				OCS Heart Population
Parameter	Statistic	OCS (N=61) n (%)	Control (N=62) n (%)	p-value	OCS (N=67) n (%)
Age (years)	N	58	62	0.4509	64
	Mean (SD)	36.09 (12.81)	34.36 (12.20)		35.43 (12.65)
	Median	35.61	33.61		35.29
	Min, Max	18.0, 57.9	13.4, 59.6		18.0, 57.9

Gender				0.6992	
Male	n (%)	41 (67.2)	44 (71.0)		44 (65.7)
Female	n (%)	20 (32.8)	18 (29.0)		23 (34.3)
Race				0.3140	
American Indian or Alaskan Native	n (%)	2 (3.4)	0 (0.0)		2 (3.1)
Asian	n (%)	3 (5.2)	1 (1.7)		3 (4.7)
Black of African American	n (%)	11 (19.0)	6 (10.2)		13 (20.3)
Hispanic	n (%)	16 (27.6)	22 (37.3)		16 (25.0)
Native Hawaiian or Other Pacific Islander	n (%)	0 (0.0)	0 (0.0)		0 (0.0)
White	n (%)	24 (41.4)	29 (49.2)		27 (42.2)
Other	n (%)	2 (3.4)	1 (1.7)		3 (4.7)
Unknown	N	3	3		3
Blood Type					
O	n (%)	34 (55.7)	31 (50.0)	0.9328	36 (53.7)
A	n (%)	20 (32.8)	23 (37.1)		24 (35.8)
B	n (%)	5 (8.2)	6 (9.7)		5 (7.5)
AB	n (%)	2 (3.3)	2 (3.2)		2 (3.0)

Overall, pre-procurement characteristics were similar between OCS Heart and SOC hearts. Only one donor heart in the SOC group had an ejection fraction (EF) < 50%.

Baseline characteristics of the OCS Heart Transplanted Donor heart population were the same as the baseline characteristics of the entire OCS Heart population.

7.1.5 Procurement, Transport, and Transplantation Characteristics

Cardioplegia and Preservation Solutions

Custodiol HTK solution was the cardioplegia solution used to effect cardiac standstill in 80% of OCS Heart-preserved hearts but only in 6.6% of SOC-preserved hearts. Conversely, University of Wisconsin (UW) solution (labelled "Other cardioplegia type") was used to preserve over 40% of SOC donor hearts. University of Wisconsin (UW) is an "intracellular" (high potassium) type solution, and Custodiol HTK is an "extracellular" (low potassium) type solution. There are differences with their constituents; for example, HTK has histidine as a primary buffer. FDA did not allow the use of non-approved solutions with the OCS Heart during the IDE, and this regulatory requirement may explain the cardioplegia differences between the treatment arms. Initial and terminal cardioplegia solution uses are shown in Tables 11 and 12.

Table 11: Initial Cardioplegia Solution at Donor Site

		Transplanted Donor Heart Population		OCS Heart Population
Parameter	Statistic	OCS Heart (N=61) n (%)	Control (N=62) n (%)	OCS Heart (N=67) n (%)
Cardioplegia Type				
St. Thomas I	n (%)	3 (4.9)	0 (0.0)	3 (4.5)
HTK (Custodial)	n (%)	49 (80.3)	4 (6.6)	53 (79.1)
Celsior	n (%)	0 (0.0)	8 (13.1)	0 (0.0)
Plegisol	n (%)	6 (9.8)	1 (1.6)	8 (11.9)
Site-specific Formula	n (%)	1 (1.6)	22 (36.1)	1 (1.5)
Other	n (%)	2 (3.3)	26 (42.6)	2 (3.0)
Unknown	n	0	1	0
Cardioplegia Volume (ml)	n	60	58	66
	Mean (SD)	606.8 (291.4)	1040.7 (284.9)	633.5 (301.3)
	Median	500.0	1000.0	500.0

Table 12: Terminal Cardioplegia Solution at Transplant Site after OCS Heart

		Transplanted Donor Heart Population	OCS Heart Population
Parameter	Statistic	OCS Heart (N=61)	OCS Heart (N=67)
Cardioplegia Type			
St. Thomas I	n (%)	2 (3.3)	2 (3.0)
HTK (Custodial)	n (%)	40 (65.6)	43 (64.2)
Celsior	n (%)		1 (1.5)
Plegisol	n (%)	6 (9.8)	8 (11.9)
Site-specific Formula	n (%)	1 (1.6)	1 (1.5)
Other	n (%)	12 (19.7)	12 (17.9)
Unknown	n	0	0
Cardioplegia Volume (ml)	n	61	66
	Mean (SD)	913.9 (189.3)	915.2 (186.0)
	Median	1000	1000
	Range	200 - 1000	200 - 1000

FDA Comment: In contrast to PROCEED II, all EXPAND (and EXPAND CAP) donor hearts received del Nido solution, a 4:1 crystalloid:blood extracellular cardioplegia.

Induction Immunosuppression

The rates of induction immunosuppression with CD25 monoclonal antibodies (basiliximab and daclizumab) and antithymocyte globulin (rabbit or equine ATG) were similar between the study groups (Table 13).

Table 13: Induction Immunosuppression

	OCS Heart (n=62)	SOC (n=66)
Monoclonal antibodies	8 (12.9%)	10 (15.2%)
Antithymocyte globulin	11 (17.7%)	11 (16.7%)

Out-of-Body Time

Table 14 shows the donor heart out-of-body times (the period from the donor cross-clamp application to recipient cross-clamp removal).

- The average OCS Heart out-of-body time was 5.4 hours. The OCS perfusion time was approximately 3.5 hours plus an average additional cold ischemia time of ~2 hours.
- The average SOC out-of-body time (i.e., cold ischemia time) was approximately 3.25 hours.

The donor out-of-body times were clinically and statistically significantly longer for OCS Heart-preserved hearts compared to SOC (Table 14).

Table 14: Donor Heart Out-of-Body Time PROCEED II

Parameter	Statistic	OCS (N=62)	Control (N=66)	p-value [1]
Pre-OCS Ischemic Time (mins)	N	61	n/a	
	Mean (SD)	30.0 (8.2)		
	Median	29		
	Min, Max	16 - 64		
OCS Perfusion Time (mins)	n	61	n/a	
	Mean (SD)	212.1 (74.6)		
	Median	200		
	Min - Max	56 - 420		
Post-OCS Ischemic Time (mins)	n	61	n/a	
	Mean (SD)	82.0 (22.7)		
	Median	84		
	Min - Max	36 - 142		

Total Cold Ischemia Time (mins)	N	61	66	
	Mean (SD)	112.0 (24.5)	196.2 (65.3)	<0.0001
	Median	118	189	
	Min, Max	62 - 169	72 - 461	
Out of Body Time (min)	N	61	66	
	Mean (SD)	324.1 (78.6)	196.2 (65.3)	<0.0001
	Median	315	189	
	Min, Max	149 - 543	72 - 461	

1 OCS times are excluded; 1 due to the (b) user error
(1) p-value is from the two-sample t-test, testing for a difference in means between treatments

FDA Comment: The OCS Heart device was associated with substantially longer out-of-body times. The increased time was likely due in part to the required relatively complex instrumentation compared to placing an organ in a cooler. The benefit-risk profile for OCS Heart, as compared to SOC, may not be constant over time of preservation.

7.1.6 Study Results

Effectiveness Results

Primary Study Endpoint

Table 15: Primary Study Endpoint – Patient and Graft Survival without MCS at Day 30 Post-Transplantation

Analysis Population		OCS Heart	SOC	95% UCB* of Difference
PP	Proportion (n/N)	0.93 (56/60)	0.97 (59/61)	
	95% CI of Proportion	0.838-0.982	0.887-0.996	0.099
AT	Proportion (n/N)	0.94 (58/62)	0.97 (64/66)	
	95% CI of Proportion	0.843-0.982	0.895-0.996	0.096
ITT**	Proportion (n/N)	0.94 (63/67)	0.97 (61/63)	
	95% CI of Proportion	0.884-0.997	0.925-1.000	0.088

*Upper confidence bound (UCB)
**Missing endpoint data imputed for OCS Heart subjects (b) (6) and (b) (6) (screen failure and termination, respectively, after turn-down of OCS Heart-transported hearts)

The pre-specified Primary Study Endpoint was met for non-inferiority (95% upper confidence bound (UCB) of difference < 0.10). Superiority was not demonstrated, and the numerical results modestly favored the

SOC group.

Success rates at 30 days were high in both arms of the study. All Primary Study Endpoint failures were due to patient death. CRFs and source documentation identified the following causes of death:

OCS Heart

- Complications of ECMO for primary graft dysfunction (PGD) (subject (b) (6));
- Complications of protamine reaction (subject (b) (6));
- Perioperative bleeding/coagulopathy (subject (b) (6) ;
- Hyperacute rejection ((b) (6)).

Control

- Subarachnoid hemorrhage - ruptured intracranial aneurysm (subject (b) (6));
- Intracranial hemorrhage/multisystem organ failure (MSOF) - ECMO for PGD ((b) (6)).

The CEC adjudicated the death of subject (b) (6) as possibly related to the OCS Heart; all other deaths were adjudicated as not related to OCS Heart or SOC preservation.

FDA Comment: Review of the data suggests to FDA that only one death (SOC subject (b) (6)) was pathophysiologically unrelated to the cardiac transplantation procedure.

FDA's independent review of case report forms (CRFs) identified 2 additional deaths among hospitalized, OCS Heart patients that occurred shortly after the 30-day primary endpoint assessment time frame (at days 33 and 38). These deaths had not been reported to FDA by the sponsor and were not considered Primary Study Endpoint failures per the endpoint definition:

- POD 33 (readmission): cardiac tamponade and cardiac arrest (subject (b) (6) . CEC adjudicated as unrelated to OCS Heart and not cardiac-related).
- POD 38 (index hospitalization): cardiac tamponade, sepsis, and respiratory failure (subject (b) (6) , not CEC-adjudicated).

For the PP population, twice as many OCS Heart patients died within 30 days compared to SOC subjects (6.7% [4/60] vs. 3.3% [2/61]), and by POD 45, three times as many OCS Heart patients had died (10% [6/60] vs. 3.3% [2/61]).

FDA Comment: The pre-specified primary endpoint (patient and graft survival without MCS at day 30) was met for non-inferiority. The Primary Study Endpoint results did not demonstrate superiority of the OCS device vs. SOC. In FDA's opinion, non-inferiority of the OCS Heart compared to the SOC in PROCEED II has limited clinical value. Importantly, the observed primary endpoint event rates favored the SOC group, and death rates at 30 and 45 days were numerically higher in the OCS Heart group.

Secondary Effectiveness Endpoint

Rejection on POD 30

The rate of ISHLT Grade 2R or 3R acute rejection or clinically symptomatic rejection was numerically higher in patients transplanted with OCS-Hearts (17.7%) vs. SOC hearts (13.6%). There were neither clinically-driven occurrences of the rejection endpoint nor biopsy-proven grade 3R acute rejection episodes. The study failed to demonstrate non-inferiority of allograft rejection post-transplantation (Table 16).

Table 16: Incidence of Biopsy Proven ISHLT Grade 2R or 3R Acute Rejection or Clinically Symptomatic Rejection* during the 30-Day Follow-up Period (Treated Population)

Statistic	OCS (N=62)	Control (N=66)
Number Subjects with 3R	0	0
Number Subjects with 2R	11	9
n/N (p[1])	11/62 (0.177)	9/66 (0.136)
95% CI for Proportion[2]	(0.092,0.295)	(0.064,0.243)
95% Upper Confidence Limit[3]	0.1469	
p-value[4]	0.5226	

[3] Non-inferiority margin 0.10

*There were no clinically symptomatic rejections

ICU Stay

The duration of initial ICU stay was numerically longer for patients transplanted with OCS-Hearts (234 hours) vs. SOC hearts (161 hours, Table 17). Non-inferiority was not met in either protocol-specified analysis population for this endpoint.

Table 17: Length of Initial ICU Stay

Statistic	Treated Population		Completed Treatment Population	
	OCS	Control	OCS	Control
n	62	66	58	64
Mean (SD)	234.24 (349.02)	161.34 (92.10)	244.39 (358.72)	157.62 (90.84)
Median	147.05	137.09	150.67	128.23
95% Upper Confidence Limit[1]	37.68		46.92	
Min, Max	54.3, 2653.8	40.7, 447.7	54.3, 2653.8	40.7, 447.7
p-value	0.1157			

[1] Non-inferiority margin of 12 hours

Average overall length of ICU stay (inclusive of ICU re-admissions) was 37% longer for recipients in the OCS Heart group (239.8 hours) vs. the SOC group (175.2 hours, Table 18).

Table 18: ICU Re-admission and Total ICU Stay (Treated Population)

Parameter	Statistic	OCS (N=62)	Control (N=66)	p-value (1)
Readmitted to ICU?				
Yes	n (%)	4 (6.5)	3 (4.5)	0.7116
No	n (%)	58 (93.5)	63 (95.5)	
Total ICU Stay (hours)	n	62	66	
	Mean (SD)	239.80 (348.13)	175.16 (130.30)	0.1734
	Median	150.67	144.94	
	Min, Max	54.3, 2653.8	40.7, 911.8	

OCS Heart patients had longer overall hospital length-of-stay vs. SOC patients, and hospital re-admission rates were similar between groups (Table 19).

Table 19: Hospital Stay Post-Transplant (Treated Population)

Parameter	Statistic	OCS (N=62)	Control (N=66)	p-value (1)
Initial Hospital Stay (days)	n	62	66	
	Mean (SD)	19.8 (23.6)	15.4 (8.1)	0.1647
	Median	14.3	12.8	
	Min, Max	3, 187	7, 46	
Readmitted to Hospital?				
Yes	n (%)	5 (8.1)	6 (9.1)	1.0000
No	n (%)	57 (91.9)	60 (90.9)	
Total Hospital Stay (days)	n	62	66	
	Mean (SD)	20.5 (23.6)	16.0 (8.3)	0.1639
	Median	15.2	13.2	
	Min, Max	3, 187	7, 46	

Post-Transplantation Ventricular Dysfunction and MCS

There were no cases in either treatment group of MCS device use on POD 30 (a component of the Primary Study Endpoint), and the proportion of patients with CEC-adjudicated adverse events of ventricular dysfunction was similar in both arms (14.5% OCS Heart, 16.7% SOC). However, in SOC patients, MCS when needed, was typically limited to shorter-term IABP-only support. In contrast, OCS Heart patients more frequently required MCS involving combinations of IABP and higher levels of circulatory support (e.g., ECMO and/or ventricular assist devices/total artificial heart, Table 20).

Table 20: Use of Mechanical Circulatory Support Devices Post-Transplantation

Type of MCS	Study arm	n	Mean ± SD (hours)	Median (hours)	Range (hours)
IABP	OCS	6	79.2±36.5	90.6	34-111
	SOC	5	53.7±48.5	32.3	13-134
VAD	OCS	3	225±173	135.6	115-425
	SOC	1	n/a	n/a	102
ECMO	OCS	4	67.8±29.0	54	52-111
	SOC	1	n/a	n/a	313

Average cardiac output/cardiac index values are shown in Table 20. Numerically trends favored the SOC group, and cardiac index was significantly higher at POD 28 (p=0.0122, Table 21). The use of vasoactive pharmacological agents was similar.

Table 21: Post-Transplant Heart Function (Treated Population)

Parameter	Timepoint	Statistic	OCS (N=62)	Control (N=66)	p-value (1)
Cardiac Output (mL/min)	24 hrs post OR discharge	n	48	60	
		Mean (SD)	5.74 (1.43)	5.84 (1.39)	0.7306
		Median	5.50	5.85	
		Min, Max	3.4, 9.7	2.9, 9.1	
	Day 28	n	44	53	
		Mean (SD)	5.59 (1.28)	5.95 (1.66)	0.2368
		Median	5.38	5.87	
		Min, Max	3.6, 8.9	2.7, 10.6	
Cardiac Index ($L/min/m^2$)	24 hrs post OR discharge	n	49	60	
		Mean (SD)	2.97 (0.64)	3.17 (0.66)	0.1146
		Median	2.97	3.13	
		Min, Max	1.9, 4.7	1.9, 5.0	
	Day 28	n	34	43	
		Mean (SD)	2.86 (0.56)	3.31 (0.97)	0.0122
		Median	2.83	3.20	
		Min, Max	1.8, 4.3	1.6, 5.8	

FDA Comment: Compared to patients transplanted with SOC donor hearts, patients transplanted with donor hearts perfused with the OCS Heart device had a numerically greater need for MCS post-transplant, more frequent acute rejection episodes, longer ICU stays, lower cardiac indices, and longer initial hospital duration. These data suggest that patients treated with OCS Hearts had more frequent post-transplant ventricular dysfunction. These results are consistent with the numerically lower observed primary endpoint event rates and lower mortality rates at 30 and 45 days that favored the SOC group vs. the OCS Heart group.

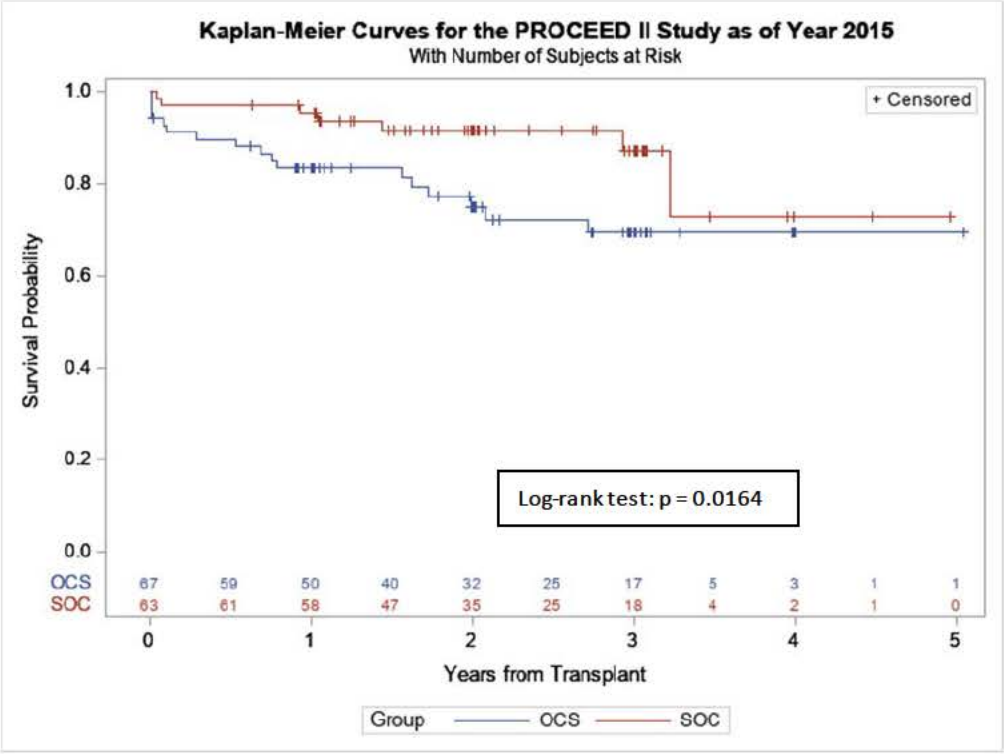
Longer-term Survival

Longer-term Survival

In 2015, FDA requested a long-term all-cause mortality survival analysis for PROCEED II's ITT population (n = 130) using SRTR data for US sites and site-contact mortality status for OUS sites.

The survival estimates for the ITT population, based upon data available to FDA in June 2015, are shown in Figure 6. Seventeen (17) OCS Heart subjects and 6 SOC subjects had died within three years of transplantation. The nominal p-value from the log-rank test was 0.0164 with survival in favor of the SOC group. As indicated by the tick marks, there was considerable censoring of survival data at that time.

Figure 6: Kaplan-Meier Analysis for All-Cause Mortality for PROCEED II Trial Patients from the Time of Transplantation, ITT Population



For the review of (b)(4), FDA requested updated longer-term PROCEED II survival follow-up. The sponsor provided data from the SRTR for the US-only As Treated population (n = 118), which represents 91% of the ITT population. Censoring at 5 years was 8.9% for OCS Heart subjects and 6.5% for SOC subjects. SOC survival probability remains higher than OCS Heart survival at all time points (Figure 7 and Table 22).

FDA calculated hazard functions for PROCEED II subjects (Figure 8). With the Cox proportional hazard model, the hazard ratio for mortality was 1.927 (95% CI: 0.987, 3.876). Testing the null hypothesis of equal survival generated a p=0.0533 for the log-rank test and p=0.0290 for the Wilcoxon test.

Figure 7: Longer-Term Kaplan-Meier Estimate of Patient Survival by Treatment Arm PROCEED II Study Subjects, As-Treated population (U.S. subgroup)

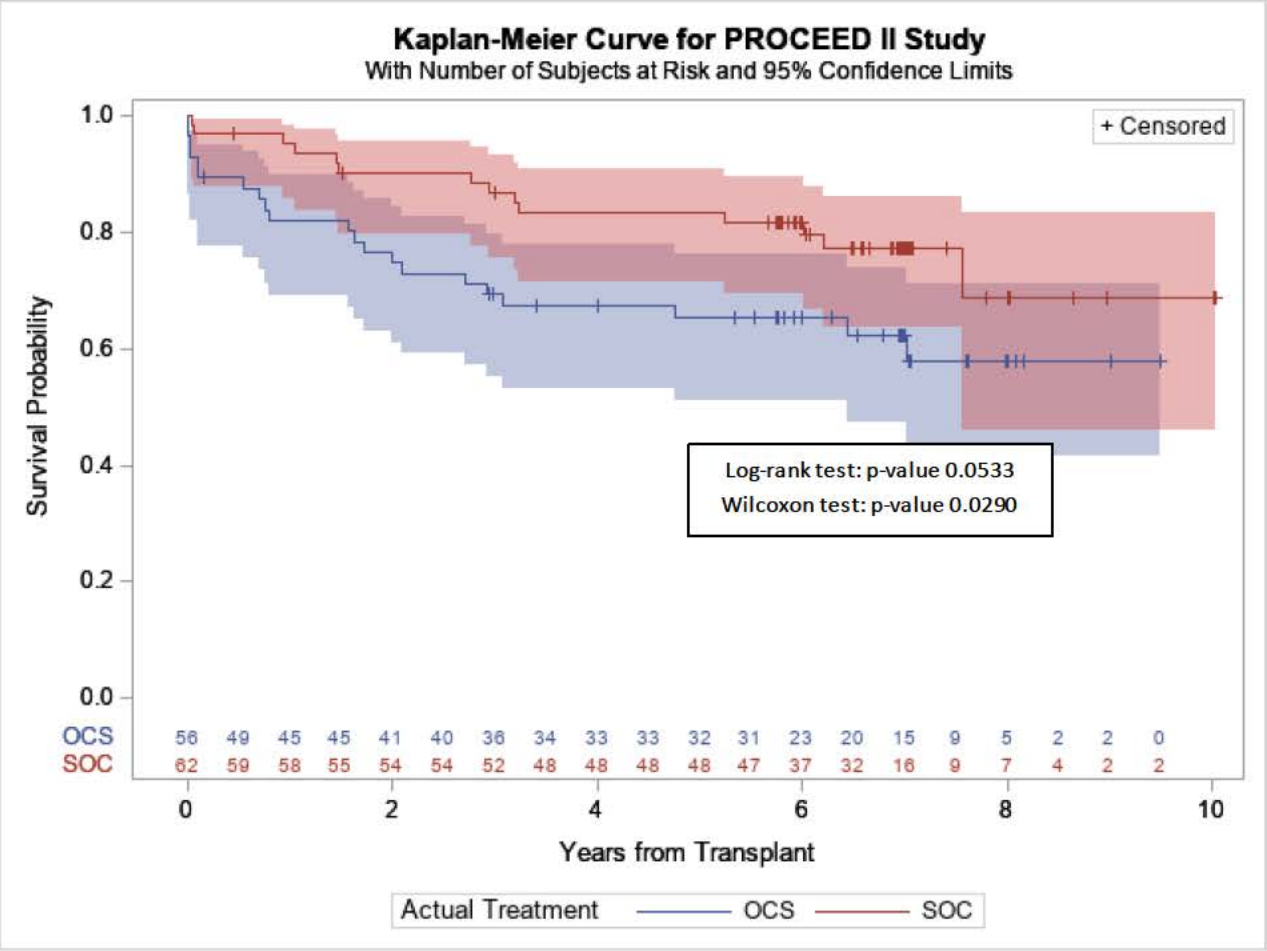


Table 22: Survival Probability PROCEED II

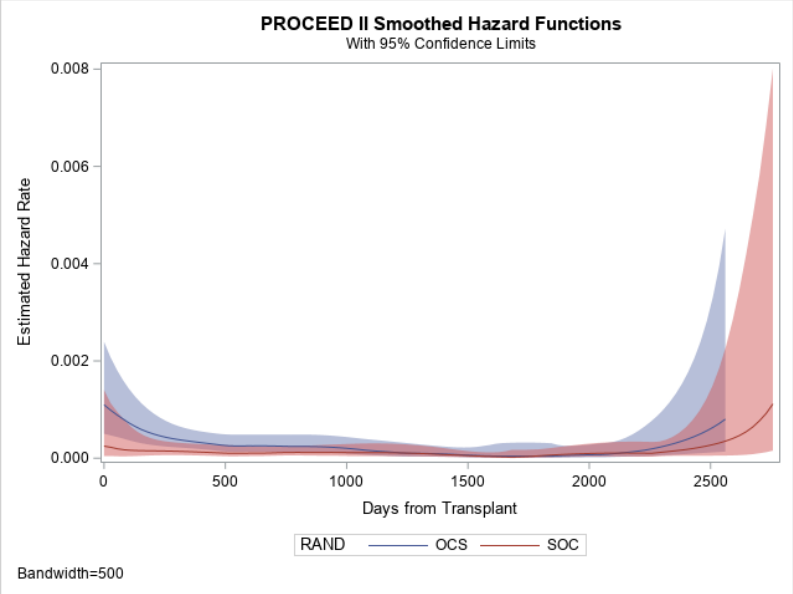
Time Post-transplantation	OCS Heart Arm (N=56)				SOC Arm (N=62)			
	Subjects Left	Censored	Died	Survival Probability % (95% CI)	Subjects Left	Censored	Died	Survival Probability % (95% CI)
6 Months	49	1	6	89.3 (77.7, 95.0)	59	1	2	96.8 (87.7, 99.2)
1 Year	45	1	10	82.0 (69.1, 89.9)	58	1	3	95.1 (85.7, 98.4)
2 Years	41	1	14	74.7 (61.1, 84.2)	54	2	6	90.2 (79.5, 95.5)
3 Years	36	3	17	69.2 (55.3, 79.6)	52	2	8	86.9 (75.5, 93.2)
4 Years	33	5	18	67.3 (53.2, 78.0)	48	4	10	83.4 (71.3, 90.7)
5 Years	32	5	19	65.3 (51.1, 76.3)	48	4	10	83.4 (71.3, 90.7)

FDA Comment: The observed all-cause mortality rate after transplantation was higher after donor heart preservation using the OCS Heart device vs. cold static preservation. The magnitude of the survival benefit for SOC was clinically meaningful and persisted over the long term.

Parametric Modelling

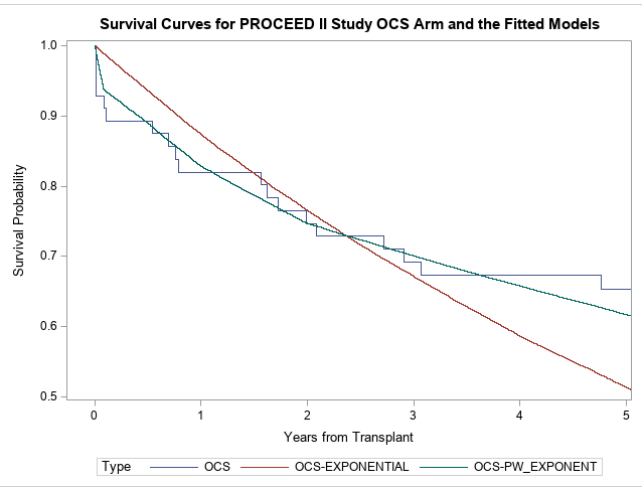
FDA built exponential and piecewise exponential models based on the PROCEED II dataset available in 2015, the time of PROCEED II's PMA submission, which had an extent of follow-up analogous to that in the current EXPAND PMA dataset. FDA compared the survival probabilities predicted by these models to the more recent PROCEED II survival rates observed in 2020 (Figure 7). The purpose of this analysis was to get some idea of how well parametric models can predict longer-term survival among cohorts of patients receiving allografts preserved with the OCS Heart device or cold static preservation. The exponential model assumes that survival time follows an exponential distribution with constant hazard rate. However, this assumption seems unlikely to hold given the shapes of the estimated hazard function plots using the 2020 PROCEED II dataset (see Figure 8 with confidence limits).

Figure 8: Estimated Hazard Function Plots PROCEED II (2020 dataset)



The piecewise exponential model assumes that the hazard rate is constant within specified time intervals and may be different between intervals. It is therefore more flexible than the exponential model. For the piece-wise exponential model, FDA specified 5 intervals (0-30 days, 31-180 days, 181-365 days, 366-730 days, and >730 days). Comparisons of the models-predicted and Kaplan-Meier-observed survival probabilities are shown in Figures 9a and 9b and Table 23.

Figure 9a: Kaplan-Meier curves and prediction for PROCEED II through 5 years



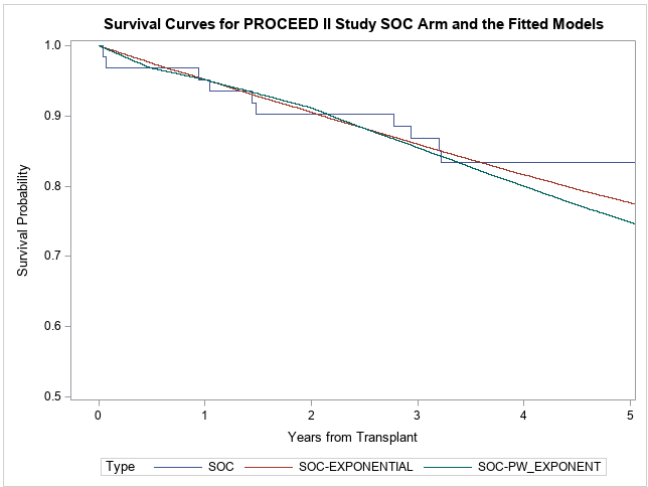
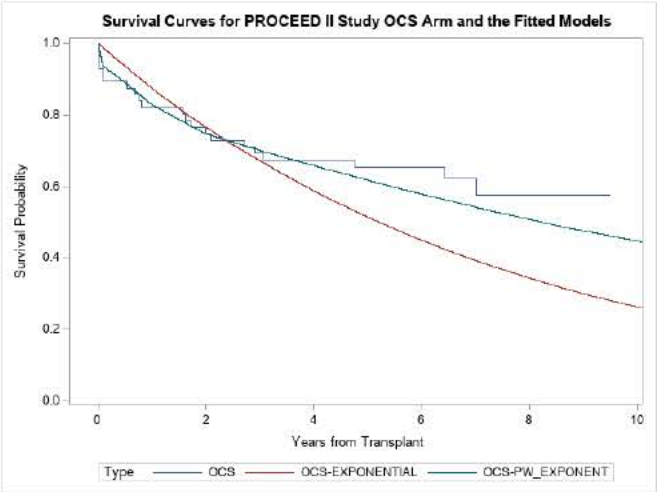


Figure 9b: Kaplan-Meier curves and prediction for PROCEED II through 10 years



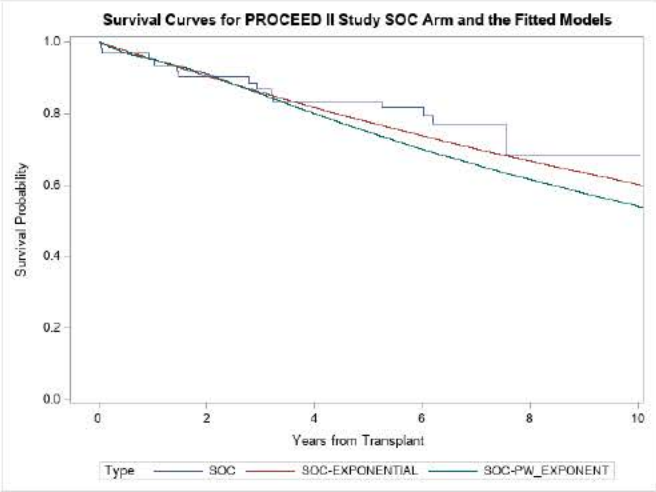


Table 23: Estimated Survival Probability PROCEED II

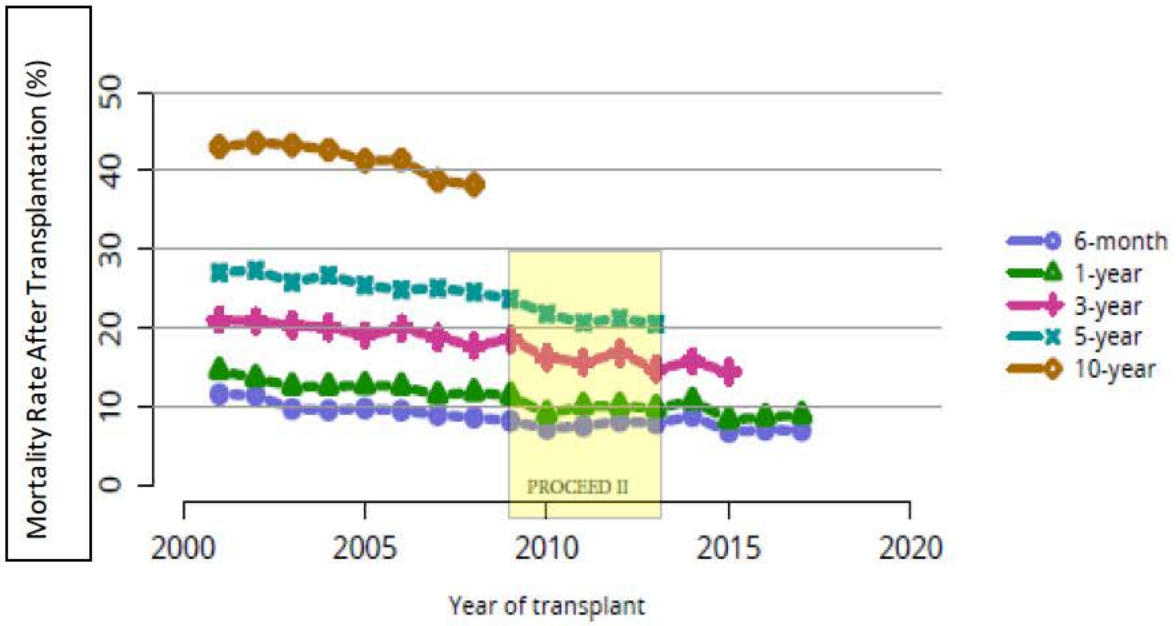
Survival Probability % (95% CI)						
Time Post-transplantation	Exponential Model* (2015 dataset)		Piecewise Exponential Model* (2015 dataset)		Kaplan-Meier (2020 dataset)	
	OCS Heart	SOC	OCS Heart	SOC	OCS Heart	SOC
1 Year	87.6 (80.8,92.1)	95.1 (89.9, 97.6)	83.0 (73.1, 91.1)	95.2 (88.7, 99.0)	82.0 (69.1, 89.9)	95.1 (85.7, 98.4)
2 Years	76.7 (65.3, 84.8)	90.4 (80.9, 95.3)	75.0 (63.3, 85.4)	91.2 (82.7, 97.0)	74.7 (61.1, 84.2)	90.2 (79.5, 95.5)
3 Years	67.2 (52.7, 80.8)	85.9 (72.7, 93.0)	70.3 (57.8, 81.9)	85.5 (73.9, 94.1)	69.2 (55.3, 79.6)	86.9 (75.5, 93.2)
4 Years	58.8 (42.6, 71.9)	81.7 (65.4, 90.8)	65.9 (50.6, 79.9)	80.2 (62.7, 92.5)	67.3 (53.2, 78.0)	83.4 (71.3, 90.7)
5 Years	51.5 (34.4, 66.2)	77.6 (58.8, 88.6)	61.8 (42.9, 78.2)	75.1 (52.6, 91.2)	65.3 (51.1, 76.3)	83.4 (71.3, 90.7)

*Fitted exponential model parameters are $\lambda = 0.0036355$ for OCS group and $\lambda = 0.0013874$ for SOC group. Fitted piecewise exponential model parameters are $\lambda = 0.00212$ (0-30days), 0.000336 (30-180days), 0.000391 (180-365days), 0.000279 (365-730days), 0.000176 (730-∞) for OCS group and $\lambda = 0.000182$ (0-180days), 0.000090 (180-365days), 0.000117 (365-730days), 0.000177 (730-∞) for SOC group.

FDA Comment: The piecewise exponential model built using the PROCEED II dataset available in 2015 worked well to predict survival during earlier time points (1-3 years), as survival probabilities based on the piecewise exponential model agree with those estimated by the Kaplan-Meier analysis of recent PROCEED II data (2020 dataset) for both SOC and OCS groups. Since the longer-term follow-up data in 2015 was sparse, the last piece of the piecewise exponential model is estimated with greater uncertainty. This explains the larger deviation of the survival probabilities based on the piecewise exponential models from those estimated by the Kaplan-Meier analysis at later time points (e.g., at 5 years). FDA used similar modeling to predict longer-term survival for the subjects enrolled in EXPAND and EXPAND CAP to provide context to the reliability of the survival probabilities (see Section 7.2.7 EXPAND Study Results and 7.3.6 EXPAND CAP Study Results).

For exploratory purposes, FDA identified the mortality data from the most recent OPTN/SRTR Annual Data Report (2018 Annual Data Report. Scientific Registry of Transplant Recipients http://srtr.transplant.hrsa.gov/annual_reports/Default.aspx, Accessed 2/4/2020) for all US transplant recipients who underwent transplantation. We present this contemporaneously with the execution of PROCEED II (2009-2013 yellow box, Figure 10).

Figure 10: Mortality Rate among Heart Transplant Recipients by Year of Transplantation



Using the Kaplan-Meier 2020 dataset in Table 22, estimates of OCS Heart mortality at one year (18%), three years (30.8%), and five years (34.7%) were numerically greater than the corresponding SRTR rates shown in Figure 12. Conversely, observed survival estimates for PROCEED II's SOC subjects were consistent with or higher than patients in the SRTR database.

Additional Post-Hoc Analyses

Preservation Time Stratification

Donor heart out-of-body time was clinically and statistically significantly longer for OCS Heart donor hearts. Tables 24 and 25 present a *post hoc* analysis of patient survival at Day 30 post-transplantation, stratified by out-of-body time, to assess the potential impact of this difference on the Primary Study Endpoint.

Table 24: Patient Survival at Day 30, Out-of-Body Time ≤ 4 hours

Analysis Population		OCS Heart	SOC	95% UCB of Difference
PP	Proportion (n/N)	0.88 (7/8)	0.98 (50/51)	
	95% CI of Proportion	0.473-0.997	0.896-1.00	0.300
AT	Proportion (n/N)	0.89 (8/9)	0.98 (53/54)	
	95% CI of Proportion	0.518-0.997	0.901-1.000	0.268
ITT	Proportion (n/N)	0.92 (11/12)	0.98 (50/51)	
	95% CI of Proportion	0.615-0.998	0.896-1.000	0.199

Table 25: Patient Survival at Day 30, Out-of-Body Time > 4 hours

Analysis Population		OCS Heart	SOC	95% UCB of Difference
PP	Proportion (n/N)	0.94 (49/52)	0.90 (9/10)	
	95% CI of Proportion	0.841-0.988	0.555-0.997	0.123
AT	Proportion (n/N)	0.94 (50/53)	0.92 (11/12)	
	95% CI of Proportion	0.843-0.988	0.615-0.998	0.115
ITT	Proportion (n/N)	0.94 (50/53)	0.92 (11/12)	
	95% CI of Proportion	0.843-0.988	0.615-0.998	0.115

In all analysis populations, point estimates for the rate of patient survival at day 30 in the OCS Heart group minimally exceeded the SOC group when out-of-body time was prolonged (> 4 hours). This finding was reversed for the study population as a whole or for the ≤ 4 hours subgroup. However, there were substantial imbalances in the out-of-body time sample sizes stratified by treatment group, and

there was only one SOC patient that failed the 30-day survival endpoint in each analysis; these factors limit any conclusions that might be drawn from these data.

FDA Comment: Inferences from the out-of-body time subgroup analysis are substantially limited by the dissimilar sample sizes and *post hoc* nature.

Covariate Adjustment for Cardioplegia Solution

FDA requested post hoc covariate adjustments to the Primary Study Endpoint result. The cardioplegia covariate added more variance and heterogeneity to the treatment difference (Table 26).

Table 26: Primary Study Endpoint Evaluation (Patient Survival at Day 30) Adjusted for Cardioplegia Solution Used

Analysis Population		OCS Heart	SOC	Adjusted 95% UCB of Difference
PP	Observed Proportion (n/N)	0.93 (56/60)	0.97 (59/61)	0.233

The protocol-specified non-inferiority margin for the full analysis dataset was 10%. The primary endpoint result was sensitive to covariate adjustment for cardioplegia (non-inferiority not met, adjusted 95% UCB of difference 0.233, Table 26). Of note, EXPAND and EXPAND CAP utilized a single cardioplegia solution that was not part of PROCEED II.

Tipping Point Sensitivity Analysis

Five OCS Heart-randomized and perfused donor hearts were turned down by investigators after preservation and transport on the OCS Heart. These hearts were consequently not part of the pre-specified effectiveness or safety analyses. It is possible that OCS Heart organs turned down by one investigator may have been implanted by another. It is also likely that had these hearts not undergone OCS Heart preservation, they would have been implanted if the preservation method had been SOC; for example, SRTR data indicate an aggregate turn-down rate of < 1% among hearts recovered for transplantation using SOC preservation.

To evaluate the impact of these turned down hearts, FDA performed two sensitivity analyses. FDA simulated the Primary Study Endpoint under the conditions of OCS Heart-preserved hearts not having been turned down after transport. A tipping point analysis was performed to assess the sensitivity of the results for the Primary Study Endpoint to all possible survival outcomes of these five hearts.

Table 26 shows the Primary Study Endpoint results when the turned-down hearts are included in the OCS Heart arm. Under the assumption that all turned-down hearts were successes, the study would continue to demonstrate non-inferiority for the Primary Study Endpoint. However, if it is assumed only one (or more) of the five hearts resulted in failure, the non-inferiority would not have been demonstrated for the Primary Study Endpoint.

Table 27: Primary Study Endpoint Statistical Results Assuming that Five Turned-Down Hearts are Added to OCS Heart Group (Additions to OCS Heart)

Analysis Set	Scenario	OCS Heart Failure	SOC Failure	95% UCB of Difference[1]	Primary Study Endpoint Success[2]
Per Protocol	0 Failures	6.15% (4/65)	3.28% (2/61)	9.05%	Yes
	1 Failure	7.69% (5/65)		11.02%	No
	2 Failures	9.23% (6/65)		12.95%	No
	3 Failures	10.77% (7/65)		14.84%	No
	4 Failures	12.31% (8/65)		16.71%	No
	5 Failures	13.85% (9/65)		18.55%	No
As Treated	0 Failures	5.97% (4/67)	3.03% (2/66)	8.83%	Yes
	1 Failure	7.46% (5/67)		10.75%	No
	2 Failures	8.96% (6/67)		12.63%	No
	3 Failures	10.45% (7/67)		14.48%	No
	4 Failures	11.94% (8/67)		16.29%	No
	5 Failures	13.43% (9/67)		18.08%	No

[1] The difference is the survival rate in the SOC arm minus the survival rate in the OCS Heart arm. Normal approximation method was used for calculating the upper confidence bound.
[2] Success if the upper limit of the 95% CI is below 10%.

Table 28 shows the Primary Study Endpoint results when the turned-down hearts are included in the SOC group. To meet the non-inferiority endpoint for the OCS Heart group, at least four of the five turned-down hearts would have had to be successes in SOC patients.

Table 28: Primary Study Endpoint Statistical Results Assuming that Five Turned-Down Hearts are Added to SOC Group (OCS Heart-to-SOC Additions)

Analysis Set	Scenario	OCS Heart Failure	SOC Failure	95% UCB of Difference[1]	Primary Study Endpoint Success[2]
As Treated	0 failure	6.45% (4/62)	2.82% (2/71)	11.21%	No
	1 failure		4.23% (3/71)	10.20%	No
	2 failure		5.63% (4/71)	8.46%	Yes
	3 failure		7.04% (5/71)	7.16%	Yes
	4 failure		8.45% (6/71)	6.98%	Yes
	5 failure		9.86% (7/71)	5.86%	Yes

[1] The difference is the survival rate in the SOC arm minus the survival rate in the OCS Heart arm. Normal approximation method was used for calculating the upper confidence bound.
[2] Success if the upper limit of the 95% CI is below 10%.

FDA Comment: The results of the sensitivity analyses suggest that the Primary Study Endpoint result is very sensitive to utilization of the five hearts, which were turned down after harvesting and perfusion with the OCS Heart.

Safety Results

There was no prespecified hypothesis-tested primary safety endpoint.

Secondary Safety Endpoint

The secondary safety endpoint (incidence of cardiac graft-related SAEs up to POD 30) demonstrated non-inferiority of OCS Heart to SOC (Table 29).

Table 29: Incidence of Cardiac Graft-Related Serious Adverse Events up to the 30-Day Follow-up Period Post-Transplant (Treated Population)

Statistic	OCS (N=62)	Control (N=66)
n/N (p[1])	8/62 (0.129)	9/66 (0.136)
95% CI for Proportion[2]	(0.057 , 0.239)	(0.064 , 0.243)
95% Upper Confidence Limit[3]	0.091	
p-value[4]	0.9028	
p-value[5]	0.0368	

[1] p=n/N = sample proportion
[2] The 95% confidence interval was calculated based on the Clopper-Pearson method.
[3] The 95% upper confidence limit is for the difference between the two population proportions (OCS - Control) and was calculated based on the normal approximation.
[4] The p-value was calculated based on the Chi-square test for a difference between the two treatment proportions.
[5] The p-value was calculated based on the noninferiority test with margin of 0.1.

More OCS Heart patients experienced adjudicated SAEs than did SOC patients (47% and 35%, respectively). Among those patients having SAEs, a numerically higher proportion of SAEs were adjudicated as cardiac graft-related SAEs in the SOC arm (39% (9/23) vs. the OCS Heart arm (28% (8/29).

Review of CEC line item data revealed that no adverse events were adjudicated as "likely" or "definitely" related to preservation methods.

FDA Comment: The rates of SAEs overall were low in both treatment arms of PROCEED II. The safety endpoint definition was modified by the sponsor during the trial.

PROTOCOL DEVIATIONS

The frequency of reported protocol violations/deviations were low and reasonable for the limited duration of follow-up. Six of the eight Major Protocol Deviations occurred in the OCS Heart arm. The majority of protocol deviations involved endomyocardial biopsies (secondary rejection endpoint).

7.2 EXPAND

7.2.1 Study Objective

EXPAND was designed to leverage the results of PROCEED II (assuming safety and effectiveness was going to be demonstrated in (b)(4)) and allow for an indication for use in non-standard criteria donor hearts. As such, in the (b)(4) submission, TransMedics states that EXPAND's purpose:

> "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 to potentially improve donor heart utilization for transplantation."

FDA informed the sponsor in August 2018 that OCS Heart effectiveness as measured by EXPAND's objectives would not, as a stand-alone dataset, provide sufficient information to support marketing approval. PROCEED II was designed to rigorously study the fundamental safety and effectiveness of the OCS Heart technology at preserving donor hearts, and FDA has not determined that the PROCEED II results provide a reasonable assurance of safety or effectiveness of the OCS Heart System for standard-criteria hearts. Therefore, FDA does not agree that inferences from EXPAND can be predicated on the OCS Heart technology having already demonstrated safety and effectiveness for standard-criteria donor hearts.

In multiple communications to the sponsor between 2014 and 2019, FDA expressed the following concerns regarding EXPAND's trial design:

- A one-arm study is less reliable than a concurrent controlled trial and is prone to potential biases. FDA therefore recommended EXPAND include a non-randomized, concurrent control arm of transplant recipients receiving standard hearts using cold storage preservation.
- FDA recommended a pre-specified, hypothesis-tested, primary safety endpoint informed by the then-available OCS Heart IDE experience and literature data.
- FDA believed it was necessary to include all eligible donor hearts in an effectiveness analysis, regardless of whether a subsequent transplant took place. This analysis would allow for important inferences regarding the OCS Heart device's ability to alter donor pool utilization in a clinically meaningful manner.

The EXPAND analysis plan did not include a comparator arm, a hypothesis-tested primary safety endpoint, or an analysis based on all subjects for whom it was determined at the donor site that there was a matching and eligible heart (similar to PROCEED II's ITT population).

FDA Comment: FDA does not believe EXPAND's analysis plan alone is sufficient to demonstrate a reasonable assurance of safety and effectiveness for OCS Heart marketing approval. Accordingly, FDA is asking the Panel to also consider the results from PROCEED II in its assessment of the OCS Heart benefit-risk profile.

7.2.2 Study Design

EXPAND was a multicenter single arm trial designed to transplant 75 donor hearts not meeting sponsor-defined standard donor heart acceptance criteria after preservation with the OCS Heart System. The trial was proposed as international, but only US sites were included.

FDA Comment: FDA recommended that EXPAND be carried out as a non-randomized concurrent controlled investigation, but this recommendation was not adopted by the sponsor.

Inclusion and Exclusion Criteria

Separate inclusion and exclusion criteria were used for prospective donor organs and consented recipients. Recipients were screened against the eligibility criteria on two occasions: (1) at the time of consent and (2) on the day of planned transplantation.

Recipient Eligibility Criteria

Inclusion

- Registered primary heart transplant candidate
- ≥ 18 years old
- Signed, written informed consent document

Exclusion

- Prior transplantation (solid organ or bone marrow)
- Chronic renal insufficiency or chronic hemodialysis
- Multi-organ transplantation

Donor Heart Eligibility Criteria

Inclusion

- Expected total cross-clamp time of ≥ 4 hours
  --or--
- Expected total cross-clamp time of ≥ 2 hours and at least one of the following:
  - 45-55 years old with no coronary catheterization data
  - ≥ 55 years old
  - Left ventricular hypertrophy (LVH): septal or posterior wall thickness > 12 and ≤ 16 mm
  - Reported down time ≥ 20 min, with stable hemodynamics
  - LV ejection fraction (EF) ≥ 40 and ≤ 50%
  - Angiographic coronary luminal irregularities: no significant coronary artery disease (CAD)
  - Carbon monoxide poisoning
  - Social history of alcoholism (EtOH)
  - Diabetes, with no angiographic CAD

Exclusion

- Angiographic CAD with > 50% stenosis
- Myocardial infarction
- Cardiogenic shock
- EF < 40%, sustained at final inspection
- Significant valve disease, not including bicuspid aortic valve

FDA Comment: EXPAND's donor heart eligibility criteria do not identify organs that are uniformly deemed unacceptable for transplantation if preserved using cold static preservation techniques. FDA believes there was overlap between hearts accepted for OCS Heart perfusion in the EXPAND and PROCEED II studies.

For recipient eligibility, EXPAND differed from PROCEED II in that the latter trial excluded candidates who had multiple prior sternotomies; were ventilator dependent; or had durable VADs complicated by sepsis, intracranial bleeding, or clinically significant sensitization.

Several donor organ eligibility criteria in EXPAND were imprecisely defined (e.g., luminal irregularities with no significant CAD, social history of alcoholism, and significant valve disease), difficult to validate (e.g., reported down time ≥ 20 min), and prone to investigator selection bias (e.g., expected total cross-clamp time of ≥ 4 hours). FDA recognized that the designation of a given donor heart as extended-criteria can be subjective and may not be reproducible across wait-listed recipients.

In its review of the original PMA submission (b)(4) (the sponsor updated the list of donor heart inclusion criteria following FDA issuance of the first deficiency letter to TransMedics dated (b)(4)), FDA noted that the most common reason for donor organ enrollment among transplanted organs was expected total cross-clamp time of ≥ 4 hours ("ECCT ≥ 4"); 29% of transplanted organs had ECCT ≥ 4 as the only criterion. Importantly, FDA considers such hearts as functionally "standard-criteria" in that they would have been eligible for PROCEED II (PROCEED II did not have a criterion defining expected cross-clamp time). FDA also noted that 8% of transplants had reported down time ≥ 20 min ("downtime ≥ 20") as the only criterion, though there were no data fields in the CRFs documenting how investigators determined the downtime duration.

FDA requested source organ procurement organization (OPO) data for all donor organs (transplanted and turned-down), as well as *post hoc* recipient survival analyses stratified by donor eligibility criteria. This information was provided after the previously locked dataset for donor eligibility was modified by the sponsor. The sponsor stated that, "While completing a careful review of our database, we determined that there were several donors that met multiple inclusion criteria; however, the investigators did not record all of the donor inclusion criteria in the Donor Eligibility eCRFs." Specifically, 17% (13/75) of transplanted donor hearts and 39% (7/18) of turned-down donor hearts had additional inclusion criteria added to the organ profiles. No donor organs had inclusion criteria removed during the sponsor's review.

FDA reviewed donor organ CRFs and source documentation in detail. FDA considers changes to the reported inclusion criteria to be problematic. Because no inclusion criteria were removed from donor hearts, it is not clear that a consistent data review was carried out for all donor organs. Furthermore, EXPAND was designed to capture eligibility as determined by the investigator at the time of organ acceptance. An investigator's decision to enroll a donor organ was inherently multi-factorial, and FDA believes it is not possible to discern retrospectively whether details within donor source documentation were in fact part of the investigator's decision-making. For example,

- The catheterization report for Donor (b) (6) stated, "40% proximal stenosis of RCA…This may actually represent the acute bend of the artery with overlap rather than actual atherosclerotic

disease." However, the investigator accepted the organ into the study for meeting the criterion of luminal irregularity.

- For Donor (b) (6), the investigator did not cite left ventricular hypertrophy (LVH) for inclusion, as the echocardiogram report was "normal," and septal thickness was 11 mm. However, the sponsor added LVH as a criterion because its review of the donor echo found posterior wall thickness to be 13 mm (the post-transplantation echo listed the posterior wall dimension as 10 mm).

FDA Comment: Although the Panel is presented with data from the modified dataset, FDA believes that donor characteristics as assessed by transplant surgeons at the time of organ acceptance are pertinent to the Panel's deliberations.

ENDPOINTS

EXPAND had a single prespecified hypothesis for the Primary Effectiveness Endpoint of transplant recipient and allograft survival at post-operative day (POD) 30 in the absence of severe primary heart graft dysfunction (PGD) in the first 24 hours post-transplantation. There were three secondary effectiveness endpoints and a single safety endpoint evaluating heart graft-related serious adverse events (SAEs). There were no hypothesis tests for the secondary effective or safety endpoints. The study was powered for the Primary Effectiveness Endpoint.

Primary Effectiveness Endpoint

The Primary Effectiveness Endpoint evaluated transplanted recipient and allograft survival at POD 30 following transplantation in the absence of severe PGD involving the left or right ventricle in the first 24 hours post-transplantation. This endpoint was tested against a performance goal of 65%. The statistical hypothesis was as follows:

$$H_O: \pi \leq 0.65$$
$$H_1: \pi > 0.65$$

where π is the proportion (lower 95% confidence interval) of subjects transplanted with an OCS Heart donor organ who survived to POD 30:

- With the originally transplanted heart, and
- Without severe LV or RV PGD, as defined by the 2014 report of the ISHLT consensus conference on primary graft dysfunction after cardiac transplantation:
  - LV:
    - Dependence on left or biventricular MCS (except IABP)
  - RV:
    - Dependence on RVAD, or
    - CI < 2.0 L/min/m^2 & RAP > 15 mmHg & PCWP < 15 mmHg & (TPG < 15 or PA systolic < 50 mmHg)

- Within 24 hours of transplantation procedure
- Not secondary to discernible cause (hyperacute rejection, pulmonary hypertension, known surgical complications)

Unlike PROCEED II, EXPAND did not include a CEC. The approved protocol indicated that a Medical Monitor (MM) would adjudicate SAEs, but it did not specifically charge the MM with adjudication of severe PGD and the Primary Effectiveness Endpoint. The protocol defined Heart Graft-Related Adverse Events (HGRAEs) as "those which have any untoward effect on the health or safety of the patient and that are related to the transplanted heart function (except for acute rejection or myocardial tamponade)," but it also defined Heart Graft-Related Serious Adverse Events (HGRSAEs), which formed the safety endpoint (see below), to include moderate PGD, severe PGD, or re-transplantation within 30 days. In this way, the analysis plan characterized the Primary Effectiveness Endpoint as a measure of an SAE, and all subjects' effectiveness outcomes were therefore determined by the MM's adjudication of investigator-assigned PGD classifications.

FDA noted that the listings of subjects with severe PGD reported to the Data and Safety Monitoring Board over the course of the trial were inconsistent with the endpoint results reported in the PMA. FDA reviewed source documentation and CRFs of all these subjects, as well as the databases containing MM decisions and DSMB deliberations. FDA observed that all PGD discrepancies between the site investigators and the MM involved the MM's downgrading investigator-assigned severe PGD to non-severe PGD; no subjects with investigator-assigned mild or moderate PGD were adjudicated by the MM as severe PGD.

FDA did not anticipate that the Primary Effectiveness Endpoint would be based upon adjudications of a single individual, the MM, who also served contemporaneously as the MM for the sponsor's 2 pivotal trials of the OCS Lung System (INSPIRE and EXPAND Lung) and as a member of EXPAND Lung's DSMB.

FDA Comment: Multiple site-identified PGD classifications were changed during the adjudication process, which took place months or years after the transplant. These changes suggest to FDA that, despite standardized definitions of PGD in EXPAND, the reported determinations were subjective to some degree. The Primary Effectiveness Endpoint result (see below) shows that the majority of endpoint failures were on the basis of PGD, not 30-day mortality. FDA does not question the MM's expertise and specific adjudications. However, the Primary Effectiveness Endpoint result should be interpreted with an understanding of the event classification changes over the course of the study and the subjectivity limitations.

The sponsor's sample size calculation anticipated an endpoint success rate of 80%. TransMedics justified the 65% PG for the Primary Effectiveness Endpoint based on a published series of PGD rates ranging between 22.6% and 32%. FDA stated a concern with the 65% PG, since the cited published studies did not utilize a standardized definition of PGD, and the proportion of extended-criteria donor organs in the historical studies was generally unknown.

Secondary Endpoints

There were 3 pre-specified secondary endpoints; 2 were components of the composite Primary Effectiveness Endpoint, and 1 evaluated the proportion of donor organs preserved with the OCS Heart that went on to be

transplanted:

- survival at POD 30 among OCS Heart transplant recipients
- incidence of severe PGD (within 24 hours) among OCS Heart transplant recipients
- utilization (i.e., transplantation) rate among OCS Heart-preserved donor organs

Safety Endpoint

The safety endpoint was the composite incidence (number of events/subject) of HGRSAEs among OCS Heart transplant recipients by POD 30. HGRSAEs were defined within Appendix 2 of the protocol and the MM charter as:

- Moderate or severe PGD per the ISHLT 2014 consensus definition
- Graft failure leading to re-transplantation

However, the protocol's Statistical Methods (analysis of safety) defined HGRSAEs differently:

- ECMO, RVAD, LVAD, BiVAD or insertion of a new IABP for >12 hours after transplant
- ≥ 2 inotropic agents/vasopressors for > 7 days after transplant
- Open chest after transplant (for compromised heart function)
- Graft failure leading to re-transplantation

The difference between the two was that the Statistical Methods definition:

- Did not require threshold hemodynamic criteria for a diagnosis of moderate PGD
- Did not require inotrope score designation
- Required a duration of > 12 hours for IABP insertion
- Classified open-chest as an additional HGRSAE

FDA reviewed line data for all subjects with HGRSAEs. FDA noted that MM adjudication disagreed with multiple investigator-classified HGRSAEs, often on the basis of the SAE timing. This could be partially due to the differences in the defined HGRSAEs as noted above.

Adverse event (AE) data collection was limited to the first 30 days after transplantation. Adjudication of AEs, including device-relatedness determinations, only applied to events recorded by POD 30. Graft failure leading to re-transplantation after POD 30 was not a component of the safety endpoint.

Subject follow-up ended at the 12-month assessment time point. Although not a part of the safety endpoint, 6- and 12-month patient and graft survival rates were pre-specified. The sponsor reported 12 subject deaths within one year of transplantation; 8 of those death events occurred after POD 30 (2 of the eight subjects had not been discharged after the index hospitalization). The sponsor indicated that the 12 subject deaths were "adjudicated by the medical monitor." The format for such adjudications is unclear to FDA, as there was no prospective collection of source documentation after 30 days.

Panel: During IDE development, FDA advised TransMedics that EXPAND's Primary Effectiveness Endpoint would likely be insufficient to capture all pertinent early safety information, and that its appropriateness as a surrogate for longer term safety was unknown. In addition, FDA recommended a hypothesis-tested primary safety endpoint. The Panel will be asked to discuss the appropriateness of EXPAND's analysis plan to support a reasonable assurance of safety.

ANALYSIS POPULATIONS

EXPAND enrollment followed a process similar to PROCEED II, except there was no randomization. Recipient consent was obtained at screening, the time of initial comparison to the pre-specified inclusion and exclusion criteria. A second assessment of recipient eligibility based upon the inclusion/exclusion criteria (i.e., a second screening of consented recipients) took place at the time investigators identified a potential donor heart meeting inclusion/exclusion criteria. Once the study site's organ procurement team confirmed donor heart eligibility with an in-chest evaluation, the recipient patient was considered enrolled.

As with PROCEED II, FDA conveyed to the sponsor that FDA considers enrollment in a device trial to occur at consent signing, defining an ITT analysis population. FDA also acknowledged that unique aspects of donor organ procurement justified an mITT population for EXPAND. FDA recommended that EXPAND include appropriately defined ITT, mITT, PP, and AT analysis populations. Prior to receiving the PMA submission, FDA indicated that analyses based on several analysis populations would be part of FDA's review, irrespective of pre-specified analysis cohorts.

Recipients

Transplanted Recipient population (TR)

All subjects who are transplanted with donor hearts preserved with the OCS Heart device, in the absence of:

- inclusion/exclusion criteria violations (donor and recipient);
- failure to follow IFU; or
- failure to follow protocol.

TR was the only pre-specified analysis population for all outcomes. TR was the same as what FDA considers to be a PP analysis population.

FDA Comment: 16% of consented and enrolled subjects were terminated from the study before undergoing transplantation. Minimal endpoint or longer-term survival data are available for these subjects. A meaningful ITT analysis, which FDA requested prior to and throughout the EXPAND Study and considers informative, is not available because of the amount of missing data.

Donor Hearts

OCS Heart population (OCS-H)

OCS-H describes all donor hearts that were instrumented onto and then transported with the device. It

includes hearts turned down for transplantation after OCS Heart preservation but excludes any hearts with day-of-surgery decisions by investigators to:

- Not procure the donor heart due to donor factors (n=4), recipient factors (n=1), or logistical factors (n=1); or
- Cross-over to cold static storage (n=1).

SCHEDULE OF ASSESSMENTS

Donor hearts

Table 30: Donor Heart Assessment Schedule

Evaluations	Donor & Heart Assessments	
	Acceptance	OCS Preservation
Eligibility & ID	X	
Demographics/Characteristics	X	
Donor Cause of Death	X	
Donor Medical & Social History	X	
Donor Heart Assessment	X	
Donor Cross Clamp Time and Flush Detail	X	
OCS Preservation Parameters		X
OCS Lactate Levels		X
Device Malfunction (if applicable)		X
Non-transplant Reasons (if applicable)		X

Recipients

Table 31: Recipient Assessment Schedule

Evaluations	Recipient Schedule of Assessments									
	Day of Tx	T 0^	T 24	T 48	T 72	Day 7	Discharge	Day 30	Mo 6	Mo 12
Eligibility & Informed Consent	X									
Demographic/Characteristics	X									
Medical & Cardiac History	X									
Transplant Details	X									
PGD Scores			X							
Inotropes Support Dose		X	X	X	X					
Right heart Catheter Data*		X	X	X	X					
Mechanical Circulatory Support		X	X	X	X	X				
Invasive Ventilator Support		X	X	X	X	X				
Patient Survival								X	X	X
Graft Survival								X	X	X
Post-Transplant ECHO*							X			
Immunosuppressive Meds & Induction (if applicable)	X					X	X			
ICU & Hospital Stay		X	X	X	X	X	X			
Heart Graft-Related AE's & SAE's	X	X	X	X	X	X	X	X		
Coronary Angiogram Results*										X

^ T0 is defined as the time of initial admission to ICU immediately post-heart transplant procedure
* ONLY Tests regularly scheduled per center standard of care or performed due to a clinical cause at these time-points will be collected.

7.2.3 Study Enrollment and Patient Accountability

Enrollment/Clinical Study Sites

To test the Primary Effectiveness Endpoint (one-sided $\alpha = 0.05$, power = 80%), the estimated sample size was 55. Of note, FDA had requested one-sided $\alpha = 0.025$. In 2017, 44 subjects had reached the Primary Effectiveness Endpoint 30-day follow-up. The sponsor requested and received approval for a sample size increase to 75 subjects "to increase confidence in the results and expand the clinical experience with the OCS Heart System in the US." The trial was approved for up to 20 US sites, and 12 sites received IRB approval and were activated. Three sites did not enroll any subjects. Previously enrolling Site 02's IRB withdrew its approval of the study in October 2017 because of unresolved study document discrepancies that "impacted study merit."

The first TR subject enrollment occurred on September 16, 2015, and the final transplantation occurred on March 25, 2018.

There were imbalances in study enrollment. Site 06 contributed 39% of the TR subjects (Table 32). Enrollment caps were not pre-specified in the study protocol, but FDA encouraged the sponsor to address EXPAND site enrollment imbalances during investigation under the EXPAND CAP study; however, this recommendation was not followed (see Appendix C, Future Consideration #2 for EXPAND CAP). Interim reports in 2019 demonstrated continued CAP enrollment dominance by Site 06 (site C01 in the CAP study), and FDA reiterated its concern about appropriate enrollment distribution. The protocol specified a poolability analysis for the Primary Effectiveness Endpoint. FDA requested *post hoc* effectiveness and survival analyses stratified by site, and the sponsor also performed a poolability analysis for survival.

Table 32: EXPAND Study Sites

#	Site Name	IRB Approval	First Use	First Transplant	Last Transplant	Transplanted Recipients (TR; n=75)
1.	(b) (6)	18-May-2015	NA	NA	NA	**0**
2		02-Jun-2015--27-Oct-2017	16-Apr-2016	16-Apr-16	4-Nov-16	**7**
3		23-Jul-2015	16-Sep-2015	16-Sep-15	27-Feb-18	**13**
4		07-May-2015	06-Sep-2016	18-Dec-16	18-Dec-16	**1**
5		30-Apr-2015	26-Jan-2016	1-Sep-16	26-Oct-16	**2**
6		09-Jul-2015	03-Jul-2016	12-Jul-16	14-Feb-18	**29**
7		26-Feb-2016	NA	NA	NA	**0**

8	(b) (6)	15-Jan-2016	24-Feb-2017	24-Feb-17	24-Feb-17	**1**
9		24-Nov-2015	29-May-2016	29-May-16	25-Feb-17	**7**
10		13-Oct-2016	20-Apr-2017	20-Apr-17	25-Mar-18	**12**
11		28-Mar-2017	10-Jan-2018	24-Feb-18	9-Mar-18	**3**
12		21-June-2017	NA	NA	NA	**0**

NA = Non-applicable due to no subjects enrolled at the site

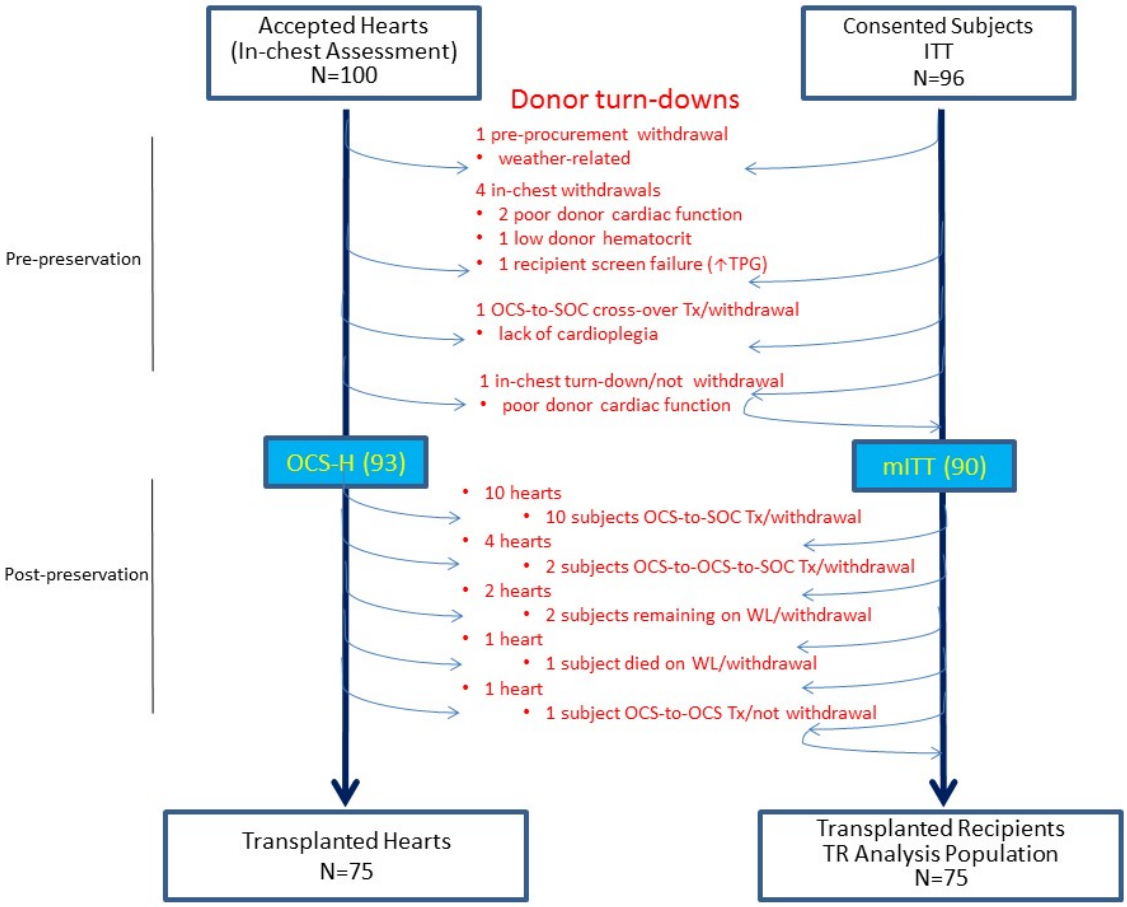
PATIENT ACCOUNTABILITY

The EXPAND Study provisionally accepted 100 hearts for 96 consented subjects:

- 7 hearts (for 7 recipients) were turned-down prior to support on the OCS Heart System
- 18 hearts (for 16 recipients) supported by the OCS Heart System were turned-down after support on the OCS Heart System but prior to transplantation
- 75 hearts supported on the OCS Heart System were transplanted into 75 recipients

Figure 11 shows EXPAND patient accountability.

Figure 11: Accountability of Identified Donor Hearts/Consented Subjects



Among the donor hearts evaluated in-chest (n=100) for consented subjects (ITT, n=96):

- One (1) heart was declined for logistical (transportation) reasons. The designated recipient was terminated from the study.
- One (1) heart was declined because the designated recipient's transpulmonary gradient was too high on the day of surgery. The subject was terminated from the study.
- Four (4) hearts were declined based upon poor function at the in-chest evaluations. Three (3) of the designated recipients went on to receive separate SOC hearts (terminated from study), and 1 subject ([(b) (6)]) went on to be transplanted on-study with a 2nd OCS Heart donor organ.
- One (1) heart that qualified on the basis of the ECCT ≥ 4 criterion could not be instrumented because the del Nido solution was unavailable. The organ was instead preserved with SOC, and the recipient ([(b) (6)]) was terminated from the study.

Fifteen (15) of 96 (16%) ITT consented subjects had donor organs accepted, procured, and transported, but no patient-level safety and effectiveness data were collected. Overall, 6 of 96 ITT subjects were excluded from mITT.

Among the procured hearts preserved with the OCS Heart device (OCS-H, n=93) and the corresponding waiting list subjects (mITT, n=90):

- Eighteen (18) hearts were turned down by investigators during or after device preservation:
  - Ten (10) of the designated recipients went on to receive separate SOC hearts and were terminated from the study.
  - Two (2) of the designated recipients were each offered 2nd OCS Heart organs that were also turned down after preservation; they went on to receive separate SOC hearts and were terminated from study.
  - One (1) designated recipient went on to receive a second on-study OCS Heart donor organ, after the first OCS Heart organ was turned down.
  - One (1) designated recipient died before transplantation.
  - Two (2) subjects remained on the waiting list at trial conclusion (two and four months, respectively, after turn-down).

Fifteen (15) of 90 mITT subjects were excluded from the TR population, because 18 hearts (19% of OCS-H) that had been deemed acceptable for transplantation at the time of procurement were turned down by investigators after device OCS Heart support. One (1) designated recipient ((b) (6)) of a turned-down heart survived at least 2.8 years after transplantation with a second OCS Heart donor organ. One (1) designated recipient ((b) (6)) subsequently died on the waiting list 2 months after study enrollment.

Consistent with previous requests (e.g., the collection of data for an ITT analysis that included subjects who received a standard of care transplant or who were not transplanted was a Major Study Design Consideration (SDC) that was communicated to the sponsor prior to initiation of EXPAND enrollment [i.e., SDC (b) in both the July 23, 2014 conditional approval letter, and the September 3, 2014 approval letter; remains unaddressed as SDC (b) in the list of remaining SDCs for the EXPAND study found in Appendix C), FDA asked the sponsor to supplement the submitted PMA data with robust ITT and mITT analyses. However, the sponsor could only generate 1-year survival status on the basis of data reported to SRTR around the time of FDAs request. Given the voluntary nature of SRTR data input, TransMedics was therefore only able to report definitive 1-year survival status for <40% of the ITT population subjects who were not part of the TR analysis population.

The absence of complete data for 21 (22%) consented EXPAND subjects and 15 (16%) enrolled subjects complicates FDA's ability to draw safety and effectiveness inferences. Although it is unknown whether hearts turned down after OCS Heart preservation, if instead implanted, would have led to sub-optimal outcomes because of underlying donor organ pathology, this possibility cannot be determined from the EXPAND dataset:

- Correlation of the observed EXPAND heart pathology findings with subject outcome is speculative, since it is generally unknown if similar anatomical findings can exist in donor hearts that are implanted and function acceptably well as an allograft.
- The experience of Subject (b) (6) (the donor heart preserved with cold static fluid) suggests that an indeterminate number of EXPAND donor organs could have been deemed appropriate by investigators for SOC preservation. In the US, < 1% of all donor hearts are turned down after SOC preservation (< 2% for donors ≥ 50 years old). The clinical outcome of EXPAND subjects who did not receive organs preserved with the OCS Heart device (i.e., recipients who received SOC hearts and recipients who remained on the waiting list) is generally unknown.
- FDA's review of the turned-down OCS-H donor hearts clinical characteristics, procurement and preservation details, and pathological reports cannot rule out that the device in some instances contributed to tissue injury and their functional correlates while on the device (e.g., elevated lactate levels, ventricular dysfunction; see Section 8).

FDA Comment: FDA is concerned that the absence of a control arm and limited data for subjects not included in a Per Protocol (PP) population (equivalent to Transplant Recipient [TR] population) makes it challenging to formulate a benefit-risk assessment for the OCS Heart.

7.2.4 Donor Heart and Recipient Demographics and Characteristics

Unless otherwise noted, data presented in Table 33 regarding donor heart and recipient demographics and clinical characteristics are derived from the sponsor's amended August 19, 2019 dataset, developed in response to an FDA request for stratification based on donor qualification criteria.

Pre-procurement Demographics

Table 33: EXPAND Pre-Procurement Demographics

Transplant Recipient population				
		Recipients (n=75)		**Donors (n=75)**
Age				
	Mean (SD)	55.46 (12.56)		37.34 (12.58)
	Median	59.22		35.99
	Min - Max	18.8 - 73.2		14.3 - 57.6
Gender				
Male	n (%)	61 (81.3)		54 (72.0)
Female	n (%)	14 (18.7)		21 (28.0)

Ethnicity				
Hispanic or Latino	n (%)	1 (1.3)		4 (5.3)
Not Hispanic or Latino	n (%)	66 (88.0)		51 (68.0)
Unknown	N	8 (10.7)		20 (26.7)
Race				
American Indian or Alaskan Native	n (%)	0		1 (1.3)
Asian	n (%)	2 (2.7)		2 (2.7)
Black of African American	n (%)	12 (16.0)		15 (20.0)
White	n (%)	58 (77.3)		55 (73.3)
Other	n (%)	2 (2.7)		0
Unknown	N	1 (1.3)		2 (2.7)
Weight (kg)				
	Mean (SD)	86.16 (19.18)		82.49 (18.5)
	Median	84.09		79.80
	Min - Max	48.0 - 140.9		42.6 - 128.0
Height (cm)				
	Mean (SD)	175.84 (9.37)		175.18 (9.93)
	Median	176.00		177.80
	Min - Max	155.0 - 195.6		149.9 - 198.0
BMI (kg/m2)				
	Mean (SD)	27.66 (4.70)		26.80 (5.25)
	Median	26.85		26.94
	Min - Max	19.1 - 42.1		18.0 - 41.3
Blood Type				
O-	n (%)	5 (6.7)		6 (8.0)
O+	n (%)	29 (38.7)		33 (44.0)
A-	n (%)	8 (10.7)		6 (8.0)
A+	n (%)	25 (33.3)		25 (33.3)
B-	n (%)	1 (1.3)		0
B+	n (%)	6 (8.0)		4 (5.3)
AB+	n (%)	1 (1.3)		1 (1.3)
Donor Final Ejection Fraction (%)	N	-		74

	Mean (SD)	-		57.4 (8.70)
	Median	-		60.0
	Min - Max	-		40 - 79
Donor Final Baseline Arterial Lactate (mmol/L)	N	-		60
	Mean (SD)	-		1.56 (0.92)
	Median	-		1.39
	Min - Max	-		0.43 - 5.43
Donor Cause of Death	N	-		75
Anoxia	n (%)	-		28 (37.3%)
Cerebrovascular/Stroke	n (%)	-		17 (22.7%)
Head Trauma	n (%)	-		25 (33.3%)
Other	n (%)	-		5 (6.7%)
Recipient Panel Reactive Antibody (%)	N	74		-
	Mean (SD)	7.9 (18.12)		-
	Median	0.0		-
	Min - Max	0 - 81		-
Recipient Listing Status	N	75		-
IA	n (%)	52 (69.3%)		-
IB	n (%)	22 (29.3%)		-
II	n (%)	1 (1.3%)		-
Recipient Diabetes	N	74		-
Yes	n (%)	29 (38.7%)		-
No	n (%)	45 (60.0%)		-
Recipient MCS	N	75		-
IABP	n (%)	11 (14.7%)		-
LVAD	n (%)	47 (62.7%)		-
BiVAD	n (%)	1 (1.3%)		-

Average recipient demographics in EXPAND were clinically similar to the OCS Heart recipients in PROCEED II, except for the following:

- EXPAND recipients were heavier and had a higher prevalence of diabetes.
- More EXPAND subjects were on MCS at the time of transplantation. Pre-transplantation use of IABP and LVAD in EXPAND was also higher than rates reported by the SRTR for 2018 (9.1% and 43.6%, respectively). FDA notes, however, that the SRTR reports similar 1-year survival after transplantation with or without pre-transplantation MCS (though longer-term survival is decreased among patients on IABP support).
- Average panel reactive antibodies (PRA) was higher in EXPAND, though this may have been the result of a few outlier subjects with very high PRAs.

Donor demographic features for donors of the transplanted EXPAND hearts (i.e., the hearts not turned down after preservation) were generally clinically similar to the donors in PROCEED II whose hearts were supported and transplanted with the OCS Heart.

7.2.5 Donor Heart Inclusion Criteria

Donor organs were accepted into the study if they fulfilled one or more of the inclusion criteria. The distribution of qualifying criteria for the OCS-H population (hearts perfused with the OCS Heart System) is shown in Table 34, stratified by whether or not the organ was transplanted at the end of the OCS Heart perfusion period. Single-criterion hearts are highlighted in gray.

Table 34: FDA Table of Revised Donor Heart Inclusion Criteria

Donor inclusion criteria OCS-H hearts (n=93)	TR hearts (n=75)	Turned-down hearts (n=18)
ECCT ≥ 4	18	3
EF ≥ 40% ≤ 50%	10	1
Downtime ≥ 20 min + EF	5	1
Downtime ≥ 20 min	4	-
Downtime ≥ 20 min + LVH	4	1
Downtime ≥ 20 min + ECCT ≥ 4	4	5
LVH (> 12 and ≤ 16 mm)	3	
Luminal irregularities, no CAD	2	1
≥ 55 y/o	2	-
ECCT ≥ 4 + EF	2	-
EtOH + ≥ 55 y/o	2	-
≥ 55 y/o + other criteria	4	-
EtOH + LVH	2	-
LVH + other criteria	5	-
ECCT ≥ 4 + ≥ 55 y/o	1	-
ECCT ≥ 4 + ≥ 55 y/o + EtOH	1	-
ECCT ≥ 4 + luminal irregularities	1	1
ECCT ≥ 4 + 45-55 y/o, no cardiac cath	1	-

Downtime ≥ 20 min + luminal irregularities	-	1
Age > 55 + downtime + luminal irregularities	-	1
Downtime ≥ 20 min + diabetes	-	1
Downtime ≥ 20 min + carbon monoxide	1	-
45-55 y/o, no cardiac cath	-	1
EtOH	1	-
EF + diabetes or EtOH	2	1

The sponsor's amended dataset led to changes in 20 OCS-H donor heart inclusion criteria. Additional criteria were assigned in all instances where donor heart inclusion criteria were revised; there were no donor hearts for which the sponsor's review identified criteria that needed to be removed. Seventeen (17) modifications changed investigators' assignment of single-criterion hearts to multiple-criteria hearts.

The proportion of transplanted EXPAND hearts accepted on the basis of only ECCT ≥ 4 in the original analysis decreased from 29% (n=22) to 24% (n=18). In the turned-down heart group, the proportion decreased from 33% (n=6) to 17% (n=3). As noted in PROCEED II, the mean and median out-of-body (or cross-clamp) times for SOC donor hearts were < 4 hours. The proportion of transplanted donor hearts defined as having only LVH changed from 17% (n=13) to 23% (n=17). FDA inquired about the justification for changing the CRF LVH output fields citing Donor (b) (6) (Subject (b) (6)) as an example. The criteria modifications were not reflected in CRF audits, and thus the clinical sites appear not to have been involved. The sponsor explained that, "Due to an unintentional oversight during database design, the eCRF only had a field for Septal Wall Thickness and it lacked a field for…left ventricular posterior wall thickness." Although donor (b) (6) echocardiogram report stated, "There is normal left ventricular wall thickness," the sponsor identified IVS and LV PW measurements of 11mm and 13mm, respectively, in the OPO's datasheets, and therefore assigned LVH on the basis of the PW dimension >12 mm. It is not clear to FDA that the investigator considered the donor organ to have LVH. Of note, the post-transplantation echocardiogram CRF showed an IVS thickness = 11 mm and LV PW thickness = 10 mm. In another example, the Donor (b) (6) (Subject (b) (6)) CRF indicates that the investigator-assigned the inclusion criterion of LVH on the basis of IVS thickness = 14 mm. The sponsor stated its database review discovered that the correct pre-procurement septal dimension was 9.5 mm, but this subject's LVH inclusion criterion was not changed to the revised analyses.

FDA Comment: It is unknown if criteria identified in a *post hoc* manner had actually informed an investigator's rationales for heart enrollment. FDA believes such changes to "extended-criteria" assignments substantially complicate the overall benefit-risk assessment of the device, because they raise questions about the true nature of the donor heart population in the study. FDA requested adjunctive analyses of endpoints and survival stratified by the inclusion criteria. However, FDA determined that the sponsor's criteria changes do not fundamentally change study-wide inferences from EXPAND's aggregate safety and effectiveness results.

7.2.6 Procurement, Transport, and Transplantation Characteristics

PRESERVATION

All procurements of the OCS-H population donor hearts occurred after an in-chest determination that the organs were functionally acceptable for transplantation. del Nido cardioplegia solution was used during both procurement and upon removal from the OCS Heart System at the recipient site. Preservation parameters for supported hearts are shown in Table 35.

Table 35: Preservation Parameters EXPAND Transplanted vs Turned-Down OCS Hearts

OCS-H Population Preservation Parameters		TR hearts (N=75)	Turned-down hearts (N=18)
Pre-OCS Ischemic Time (mins)	n	75	18
	Mean (SD)	29.7 (7.92)	30.5 (7.70)
	Median	28.0	29.0
	Min - Max	15 - 53	19 - 56
OCS Perfusion Time (mins)	n	75	18
	Mean (SD)	278.6 (83.28)	298.8 (76.87)
	Median	276.0	266.0
	Min - Max	100 - 532	220 - 500
Post-OCS Ischemic Time (mins)	n	75	0
	Mean (SD)	72.5 (21.88)	
	Median	72.0	
	Min - Max	36 - 135	
Total Ischemic Time (mins)	n	75	n/a
	Mean (SD)	102.1 (22.64)	
	Median	98.0	
	Min - Max	65 - 168	
Total "Cross Clamp" Time (min)	n	75	n/a
	Mean (SD)	380.7 (93.20)	
	Median	369.0	
	Min - Max	173 - 682	
Arterial Lactate—Pre-OCS	n	73	16
	Mean (SD)	1.3 (0.58)	1.6 (1.02)
	Median	1.1	1.2
	Min - Max	0.39 - 3.49	0.34 - 3.90

Arterial Lactate—Initial OCS	n	75	18
	Mean (SD)	1.9 (0.64)	2.2 (0.91)
	Median	1.8	2.0
	Min - Max	0.93 - 3.80	1.06 - 4.47
Arterial Lactate—Final OCS	n	75	18
	Mean (SD)	3.1 (0.95)	5.1 (0.84)
	Median	3.0	4.9
	Min - Max	0.55 - 4.97	3.50 - 7.17
AOP Mean (mmHg)	n	75	18
	Mean (SD)	81.2 (7.8)	83.2 (7.0)
	Median	81.4	83.4
	Min - Max	48 - 102	68 - 97
Coronary Flow (L/min)	n	75	18
	Mean (SD)	0.760 (0.136)	0.751 (0.166)
	Median	0.785	0.785
	Min - Max	0.06 – 0.99	0.15 - 0.92

FDA Comment: Other than an increase in the average final OCS Heart arterial lactate level, all preservation parameters and trends were similar between donor hearts that were transplanted and donor hearts that were turned down at the conclusion of OCS Heart perfusion.

PA Cannula Disconnections

FDA identified missing CF trend data for multiple OCS-H donor organs. The sponsor explained that investigators detached the device pulmonary artery (PA) outflow cannulae in 17 of 93 hearts (18%) because of concerns for right ventricular dysfunction observed during perfusion. Among the subset of 18 turned-down hearts, PA canulae disconnections occurred in 7 (39%). The PA cannula was disconnected on average for 26% of OCS Heart perfusion time (range 1% - 88%). PA canulae disconnection was not a part of the protocol and is not described in the IFU. Documentation of the disconnections was not in the CRFs or available in source documentation.

Panel: FDA does not question investigators' clinical decisions to turn down accepted organs because of concerns for poor outcomes. Overall, 13% (27/207) of accepted donor hearts included in the IDE studies were turned down by investigators after OCS Heart preservation (PROCEED II 7%, 5/69; EXPAND 19%, 18/93; EXPAND CAP 9%, 4/45). No donor hearts preserved with cold static preservation in these studies were turned down. SRTR data present an aggregate turn-down rate of < 1% among hearts recovered for transplantation. FDA is concerned that available pathology data from the IDE trials cannot rule out a causal connection between OCS Heart perfusion and myocardial injury in some cases (see Section 8). The Panel will be asked to provide an opinion on the potential correlation between OCS preservation and myocardial injury.

Induction Immunosuppression

Reported rates of induction of immunosuppression were lower than in the PROCEED II trial. The SRTR reports that ~50% of recent heart transplantations involve induction immunosuppression, although its clinical value is debated.

Table 36: Induction Immunosuppression

	EXPAND (n=75)
Monoclonal antibodies	1 (1.3%)
Antithymocyte globulin	14 (18.7%)

7.2.7 EXPAND Study Results

Effectiveness Results

Primary Effectiveness Endpoint

Table 37: Primary Effectiveness Endpoint Results

Survival at POD 30 without severe PGD (LV or RV)	TR population (N=75)	95% CI of Proportion	Performance Goal	p-value
Proportion (n/N)	88.0% (66/75)	78.4 - 94.4	65%	<0.0001*

*p-value from a one-sided exact binomial test (α=0.05)

The pre-specified Primary Effectiveness Endpoint was met. Nine (9) subjects failed the Primary Effectiveness Endpoint:

- 3 subjects developed severe PGD and died within 30 days, adjudicated as secondary to PGD:
  - POD 29: (b) (6) (68 y/o male) / (b) (6) (criterion: ≥ 55 y/o)
  - POD 18: (b) (6) (45 y/o female) / (b) (6) (criteria: downtime ≥ 20 minutes, carbon monoxide poisoning)
  - POD 12: (b) (6) (47 y/o male) / (b) (6) (criterion: LVH)
- 1 subject died within 30 days without adjudicated severe PGD:
  - POD 29: (b) (6) (65 y/o male, death adjudicated as multi-organ failure secondary to cirrhosis) / (b) (6) (criterion: ECCT ≥ 4)

- 1 subject developed severe PGD and loss of allograft secondary to PGD
  - POD 6: (b) (6) (57 y/o male, re-transplantation (off-study)) / (b) (6) (criterion: ECCT ≥ 4)
- 4 subjects developed severe PGD and were discharged (1 before and 3 after POD 30):
  - POD 26: (b) (6) (58 y/o male) / (b) (6) (criterion: EF ≥ 40% ≤ 50%)
  - POD 41: (b) (6) (37 y/o male) / (b) (6) (criterion: ECCT ≥ 4)
  - POD 57: (b) (6) (52 y/o male) / (b) (6) (criteria: downtime ≥ 20 minutes + LVH)
  - POD 115: (b) (6) (47 y/o male) / (b) (6) (criteria: downtime ≥ 20 minutes + LVH + EtOH)

Six (6) of the Primary Effectiveness Endpoint failures were for donor hearts with a single EXPAND inclusion criterion, with ECCT ≥ 4 accounting for 3 of the 6 endpoint failures.

Table 38 shows an FDA-requested *post hoc* analysis of the Primary Effectiveness Endpoint stratified by the number (single or multiple) and type of donor inclusion criteria (carbon monoxide and diabetes are not included). The study was not powered for this analysis, and the confidence intervals are wide. Subjects receiving donor organs with multiple inclusion criteria had a modestly higher proportion meeting the Primary Effectiveness Endpoint.

Table 38: Primary Effectiveness Endpoint by Donor Inclusion Criteria

Survival at POD 30 without severe PGD (LV or RV)	Single or Multiple Criteria	95% CI of Proportion	Single Criterion	95% CI of Proportion	Multiple Criteria	95% CI of Proportion
All	66/75 (88.0%)	78.4 - 94.4	34/40 (85.0%)	70.2 - 94.3	32/35 (91.4%)	76.9 - 98.2
ECCT ≥ 4	25/28 (89.3%)	71.8 - 97.7	15/18 (83.3%)	58.6 - 96.4	10/10 (100.0%)	69.2 - 100.0
EF ≥ 40% ≤ 50%	20/21 (95.2%)	76.2 - 99.9	9/10 (90.0%)	55.5 - 99.7	11/11 (100.0%)	71.5 - 100
Downtime ≥ 20 minutes	20/23 (87.0%)	66.4 - 97.2	4/4 (100.0%)	39.8 - 100.0	16/19 (84.2%)	60.4 - 96.6
LVH	14/17 (82.4%)	56.6 - 96.2	2/3 (66.7%)	9.4 - 99.2	12/14 (85.7%)	57.2 - 98.2
Luminal irregularities/no CAD	7/7 (100.0%)	59.0 - 100.0	2/2 (100.0%)	15.8 - 100.0	n/a	n/a
≥ 55 y/o	9/10 (90.0%)	55.5 - 99.7	1/2 (50.0%)	15.8 - 100.0	8/8 (100.0%)	63.1 - 100.0
EtOH	8/9 (88.9%)	51.8 - 99.7	1/1 (100%)	2.5 - 100	7/8 (87.5%)	47.3 - 99.7

Among the 9 out of 75 subjects (12%) who failed the composite Primary Effectiveness Endpoint, severe PGD was a cause in 8 out of 75 (11%; the rate of severe PGD was a secondary effectiveness endpoint).

Thirty (30)-day mortality after severe PGD occurred in 3 out of 8 subjects (38%), and 30-day mortality from any cause (the other secondary effectiveness endpoint) occurred in 4 out of 75 subjects (5.3%). Thirty (30)-day mortality and/or loss of allograft occurred in 4 out of 8 subjects (50%) with observed severe PGD events.

There are few published, prospective series on PGD rates and sequelae since the adoption of the ISHLT 2014 definition. A United Kingdom national study (1) identified a severe LV PGD rate of 18% and RV PGD rate of 1% among 450 heart transplant recipients between 2012 and 2015. The 30-day mortality for patients with any PGD (mild, moderate, or severe) was 19%, while severe LV PGD had a 30% 30-day mortality; 30-day mortality in the absence of any PGD was 4.5%. A Canadian study (2) identified severe LV PGD in 3.9% and RV PGD in 2.9% of 412 heart transplantations (2014 ISHLT definition). A single-center, retrospective study of 191 isolated heart transplantations (3) identified severe LV PGD in 8.4% recipients, with a 30-day mortality rate of 38%; the 30-day mortality in the absence of any PGD was 0%.

FDA Comment: Although the appropriateness of the performance goal value (65%) for the Primary Effectiveness Endpoint was uncertain at the time the study was designed, the study met the endpoint. FDA believes the observed result, which represents a short-term assessment, is comparable to published series.

Secondary Endpoints

Donor Heart Utilization and Post Hoc Analysis: Sensitivity to Turned Down Hearts

The donor heart utilization rate after preservation was 80.6% (turn-down rate: 19.4%). Site-specific turn-down rates in EXPAND varied between 0% and 60%. Heart turn-down rates at the three highest-enrolling sites (03, 09, and 06) were 19%, 19%, and 15%, respectively. The heart turn-down rate in the ongoing CAP study is 9%.

To address the impact of turn-down decisions (i.e., utilization rate) on the Primary Effectiveness Endpoint result, FDA evaluated the Primary Effectiveness Endpoint under the conditions of OCS Heart-preserved hearts not having been turned down after transport. A tipping point analysis was performed to assess the sensitivity of the results for the Primary Study Endpoint to all possible survival outcomes of these 18 hearts.

The Primary Effectiveness Endpoint result was not sensitive to turned-down hearts. Fifteen (15) additional failures would be needed to change the statistical result (Figure 12 - *Green: Reject the null hypothesis, Red: Null hypothesis not rejected (one-sided 0.025 significance level)*

Figure 12 Primary Effectiveness Endpoint Sensitivity to Turned-Down Hearts

	Number of Failure in Turned-Down Hearts																		
Adding 18 hearts to the study	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**

Incidence of Severe PGD (LV or RV)

The incidence of severe PGD was 10.7%, consistent with published reports (Table 39).

Table 39: Incidence of Severe PGD

Incidence of severe PGD (LV or RV)	TR population (N=75)	95% CI of Proportion
Proportion (n/N)	10.7% (8/75)	4.7 - 19.9

The Safety Endpoint captures the rate of moderate and severe PGD. Moderate LV PGD is a clinical entity that also adversely affects post-transplant patient survival. Adjudication of PGD in accordance with the 2014 ISHLT framework strictly differentiates between moderate and severe LV PGD. FDA identified several subjects (e.g., (b) (6), (b) (6), (b) (6)) that successfully met the primary endpoint (no severe LV PGD) but nonetheless experienced clinically significant allograft dysfunction within the first 24 hours (e.g., Subject (b) (6) required intraoperative ECMO in order to separate from CPB).

Patient Survival at Day 30 Post-transplantation: See Table 40.

Table 40: Patient Survival at POD 30

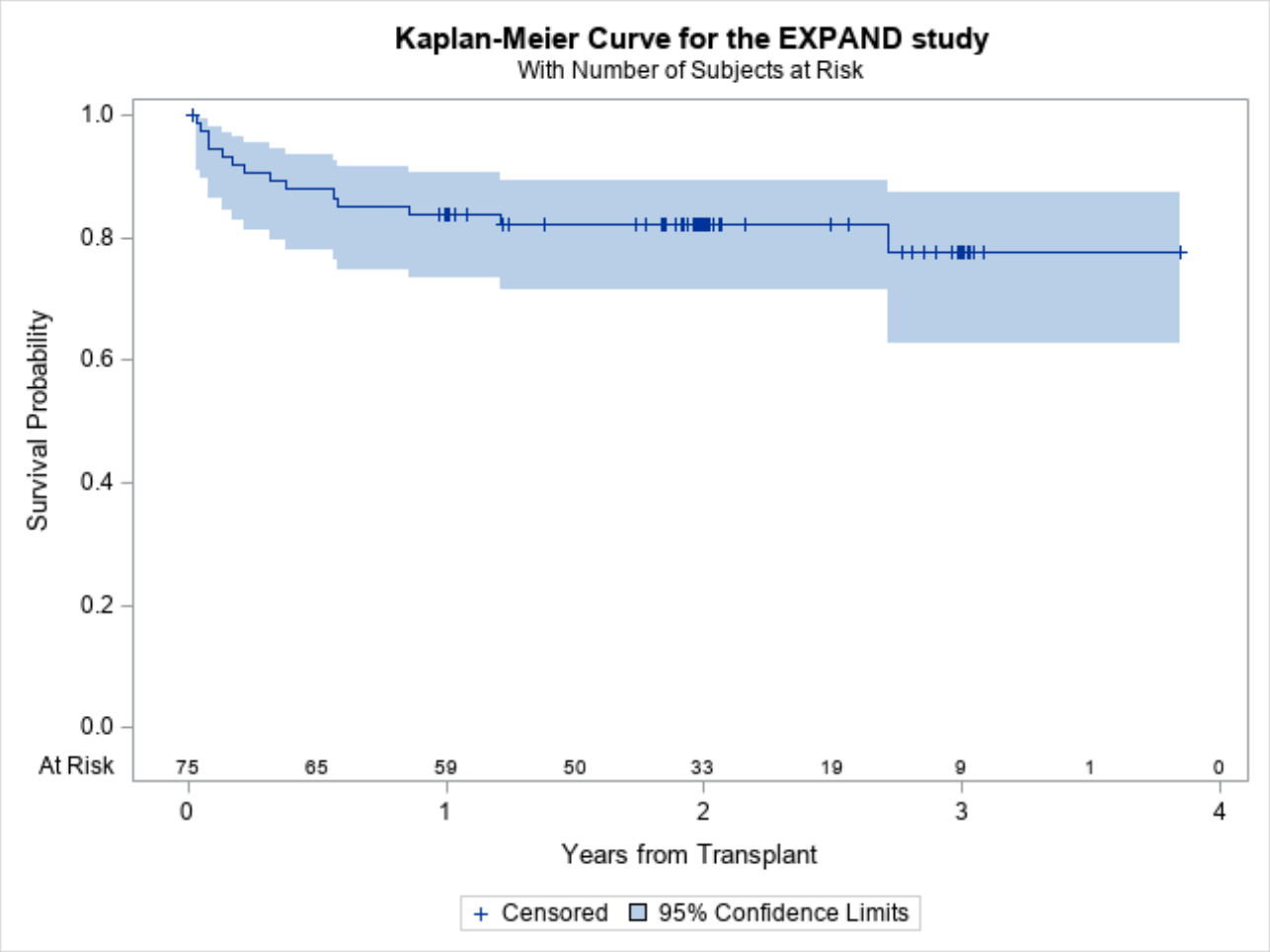
Patient Survival at POD 30	TR population (N=75)	95% CI of Proportion
Proportion (n/N)	94.7% (71/75)	86.9 - 98.5

LONGER-TERM SURVIVAL

A 12-month survival analysis was pre-specified in the protocol for the TR population. The sponsor reported a one-year survival of 84% (63/75). One additional subject ((b) (6)) who underwent re-transplantation (using SOC preservation) on post-operative day (POD) 6 was terminated from the study and had reported survival to one year. Although subjects had consented for 1-year follow-up, FDA stressed early in interactions with the sponsor that they obtain longer-term follow-up for EXPAND subjects given FDA's concern with the survival results observed in PROCEED II. All EXPAND subjects reached the 18-month time point by November 2019, and all reached the 2-year follow-up time point by March 2020. The sponsor obtained survival status from the SRTR database in February 2020; 18-month survival data were censored for 12/75 (16%), and 2-year survival data were censored for 32/75 (43%).

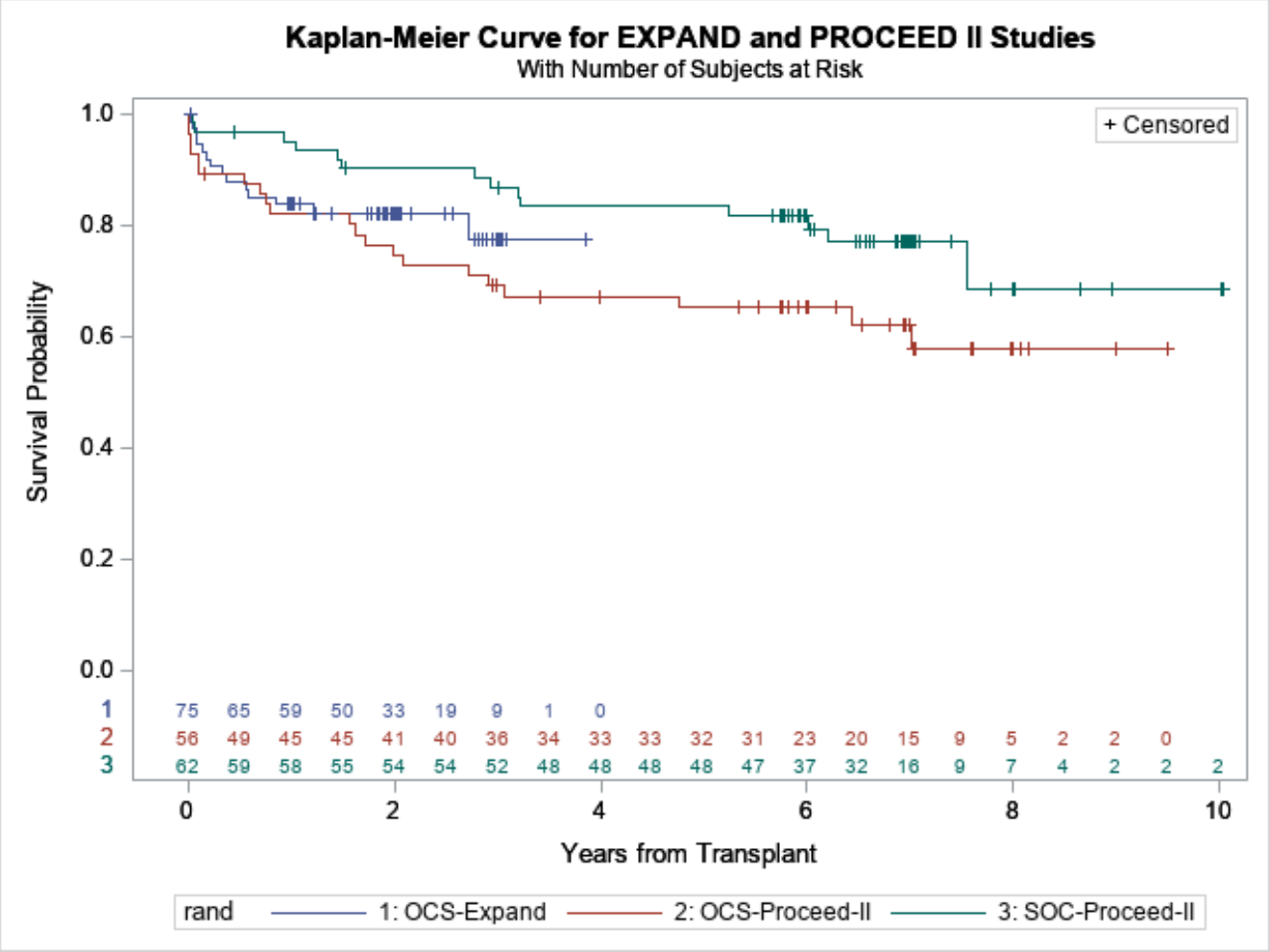
The Kaplan-Meier survival analysis for EXPAND is shown in Figure 13, demonstrating survival rates of 83.8% at 1-year, 82.2% at 2 years, and 77.7% at 3-years.

Figure 13: Kaplan-Meier Curve for EXPAND



As previously discussed, the sponsor generated PROCEED II Kaplan-Meier survival analyses with updated SRTR survival data; there was minimal censoring of those data. The updated PROCEED II and EXPAND survival curves are presented together in Figure 14.

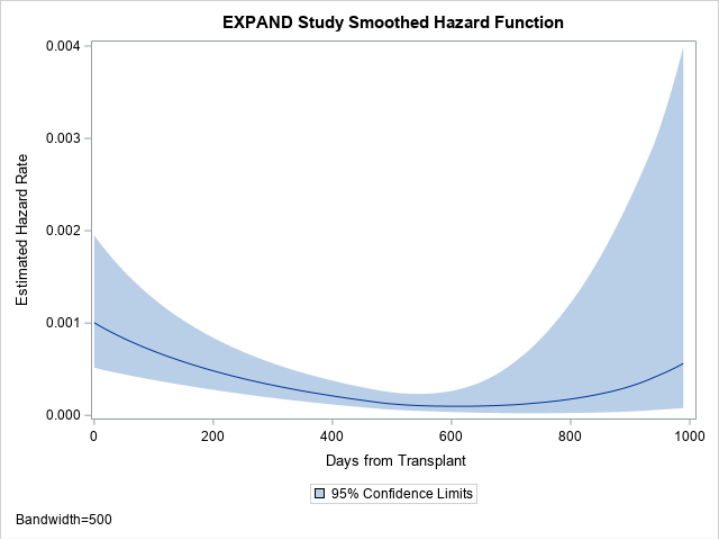
Figure 14: Kaplan-Meier Curves for EXPAND and PROCEED II



HAZARD FUNCTION AND FITTED PARAMETRIC MODELLING

The EXPAND survival curve (Figure 14) shows an early hazard function similar to PROCEED II's OCS Heart arm, but with some separation of the survival curves at approximately 2 years. However, this observation should be interpreted with caution; as shown by the EXPAND tick marks, there was substantial censoring, which is illustrated by the widening confidence intervals of the hazard function beginning at 2 years (Figure 15).

Figure 15 EXPAND Smoothed Hazard Function



Accordingly, to estimate the longer-term survival rates, we applied the Exponential and Piecewise exponential models to the available EXPAND data, similar to how survival probabilities were predicted for PROCEED II (Figure 16 and Table 41).

Figure 16: Survival Curves for EXPAND and Fitted Models

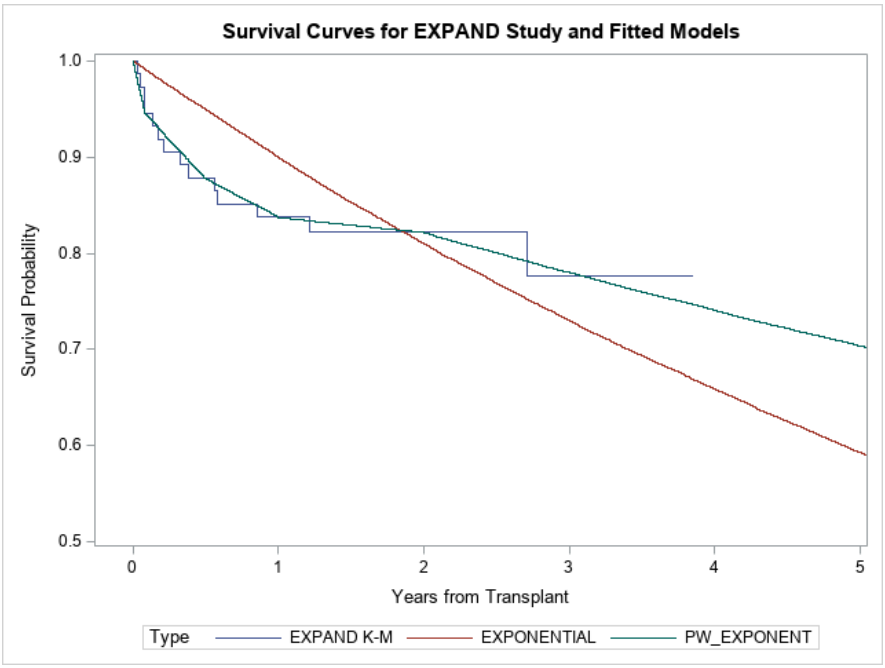


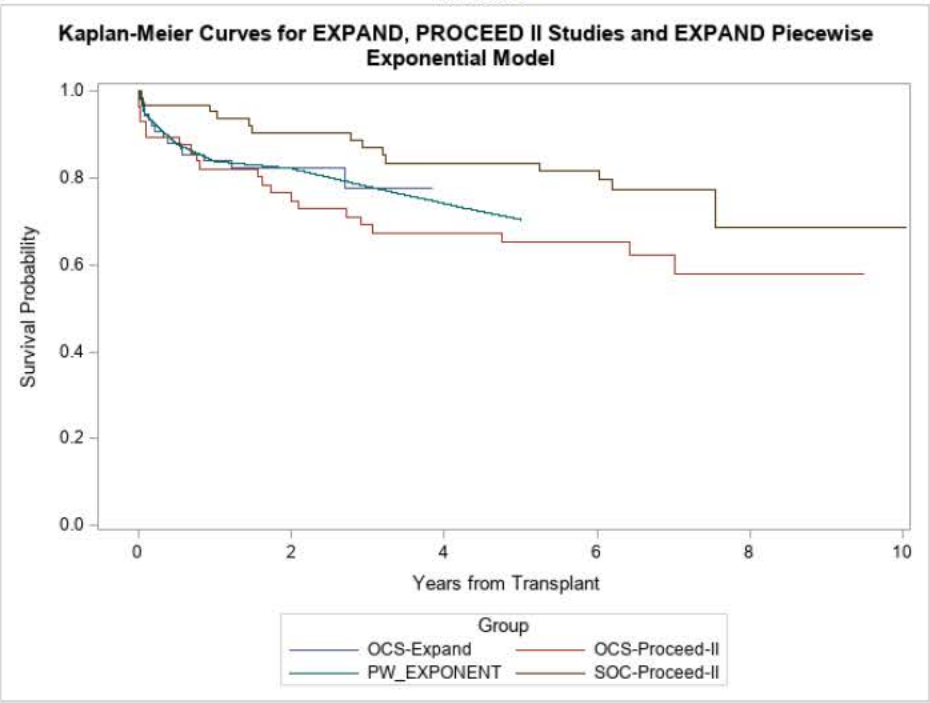
Table 41: EXPAND Survival Probabilities

Time Post-transplantation	Survival Probability % (95% CI)		
	Exponential Model*	Piecewise Model*	Kaplan-Meier
1 Year	90.1 (83.9, 94.0)	83.8 (74.7, 91.2)	83.8 (73.2, 90.5)
2 Years	81.2 (70.3, 88.4)	82.1 (72.8, 90.0)	82.2 (71.4, 89.3)
3 Years	73.1 (59.0, 83.1)	78.0 (65.5, 87.8)	77.7 (62.7, 87.2)
4 Years	65.9 (49.4, 78.1)	74.1 (55.4, 86.8)	-
5 Years	59.4 (41.5, 73.4)	70.4 (46.1, 86.1)	-

*Fitted exponential model parameter is λ=0.00028581. Fitted piecewise exponential model parameters are λ= 0.00183 (0-30days), 0.000498 (30-180days), 0.000258 (180-365days), 0.000056 (365-730days), 0.000140 (730-∞).

The piecewise exponential model shows good agreement with the Kaplan-Meier estimates for EXPAND and provides an estimate of longer-term survival for EXPAND subjects. Figure 17 provides a combined plot that includes Kaplan-Meier curves for PROCEED II and EXPAND with a prediction for EXPAND.

Figure 17 Kaplan-Meier Curves for EXPAND, PROCEED II, EXPAND Piecewise Exponential Model



Based on the piecewise exponential model, three (3) year survival for EXPAND subjects is expected to be 78%; by comparison, the SRTR reports that 3-year survival for US patients who underwent heart transplantation between 2011 and 2013 was 85%. Based on the same model, five (5) year survival among EXPAND subjects is expected to be 70%; by comparison, 5-year survival for US subjects in the SRTR database was 80%. FDA acknowledges that modeling of longer-term EXPAND survival may evolve as more complete mid-term survival data become available.

FDA Comment: Based upon the currently available data and modeling, longer-term survival for EXPAND subjects receiving extended-criteria donor hearts preserved using the OCS Heart may be similar to the survival observed in recipients of standard donor hearts preserved with the OCS Heart during PROCEED II. The survival rate appears to be lower than the survival of SOC subjects in PROCEED II.

Transplant Waiting List Times

Table 42 compares the TR population demographics and median waiting list times to those of the SRTR transplant recipients (2018 data). EXPAND's distributions of blood type and urgency status were similar to the SRTR's. A higher proportion of EXPAND recipients were on LVAD or IABP support at the time of surgery.

Median time on the transplant list was approximately two months shorter for EXPAND than the SRTR group. The majority of waiting time decrement was accrued by blood type O subjects, the blood group which generally experiences the longest wait times. The decision by subjects to enroll (consent) in the EXPAND study was made after a median of 2-3 months on the waiting list. Once consented, half of the TR subjects had received their transplanted organs within an additional 1.5 months of waiting.

Table 42: Wait List Times

Waiting List Times	EXPAND TR (n=75)	SRTR 2017-2018 (n=2967)
Days on WL prior to transplant (median)		
All	138 (100%)	207 (100%)
Blood type		
O	151 (45%)	405 (40%)
A	126 (44%)	150 (39%)
B	146 (9%)	132 (16%)
AB	122 (1%)	45 (5%)
Urgency		
Status 1A	138 (69%)	59 (66%)
Status 1B	117 (29%)	216 (31%)
Status 2	186 (1%)	507 (3%)
Circulatory support at transplant		

IABP	15%	9%
LVAD	63%	44%
BiVAD	1%	<1%
RVAD/ECMO/TAH	0	5%
Days on WL prior to EXPAND consent (median)		
All	81	-
O	60	-
A	91	-
B	56	-
AB	121	-
Urgency		
Status 1A	77	
Status 1B	71	
Status 2	185	
Circulatory support at transplant		
IABP	57	
LVAD	113	
BiVAD	7	
Days on WL after EXPAND consent (median)		
All	35	
O	41	
A	22	
B	30	
AB	1	
Urgency		
Status 1A	35	
Status 1B	33	
Status 2	1	
Circulatory support at transplant		
IABP	34	
LVAD	41	
BiVAD	40	

Panel: According to the SRTR, 33% of newly listed patients undergo transplantation within 3 months, and 57% undergo transplantation within one year. Within a year of listing, approximately 16% of subjects either die while waiting for a donor organ or are removed from the list. The OCS Heart group had shorter wait times than patients in the SRTR. However, EXPAND was not prospectively designed to use the SRTR as a comparator to assess wait times (for which other factors may also be considered). The Panel will be asked to discuss potentially shorter wait times for an extended-criteria donor heart in the context of post-transplantation outcomes including post-transplant survival.

POST-TRANSPLANT FUNCTIONAL ASSESSMENTS

Mechanical Circulatory Support Post-Transplant

The use of MCS postoperatively in EXPAND is shown in Table 43.

Table 43: Post-Operative MCS Support EXPAND

Mechanical Circulatory Support Post-Transplant	Percentage of Subjects (n/N)	Duration of Support (hours) Mean ± SD
Mechanical Circulatory Support	26.7% (20/75)	
RVAD	2.7% (2/75)	219.12 ± 31.35
LVAD	2.7% (2/75)	139.0 ± 93.34
IABP	18.7% (14/75)	80.0 ± 63.20
ECMO	12.0% (9/75)	132.04 ± 97.09
BiVAD	0% (0/75)	--
Percentages are calculated based on the number of subjects in the Transplanted Recipient Population with non-missing data. A recipient may have more than type of post-transplant support, so the percentages may sum to more than 100%. Note: The duration of support is the sum of the durations of all periods of support.		

The postoperative MCS use rate in EXPAND was greater than the rates for either the OCS Heart or SOC group for PROCEED II (see Table 20).

Initial ICU and Hospital Stays Post-Transplant

ICU and hospital stays for EXPAND are shown in Table 44.

Table 44: ICU and Hospital Stays (index)

Length of Initial Post-Transplant ICU Stay (Hours)	OCS (N=75)
Mean ± SD	316.8 ± 420.38
Median	199.9
Min.- Max.	55.4 – 2679.5
Length of Initial Post-Transplant Hospital Stay (Hours)	**OCS (N=74)**
Mean ± SD	666.68 ± 554.36
Median	515.09
Min.- Max.	211.42 – 3043.05

Median and Mean ICU and hospital stays were longer for EXPAND subjects than either the OCS Heart or the SOC group of PROCEED II (see Tables 17 through 19).

Safety Endpoint

There was no pre-specified primary safety endpoint hypothesis test.

Secondary Safety Endpoint

The safety endpoint was based upon the occurrence of adjudicated HGRSAEs (Table 45).

Table 45: Heart Graft-Related SAEs

HEART GRAFT-RELATED SERIOUS ADVERSE EVENTS UP TO 30 DAYS AFTER TRANSPLANTATION
TRANSPLANTED RECIPIENT POPULATION

Type of HGRSAE	OCS (N=75)
At Least One HGRSAE	12 (16.0%)
Severe LV PGD	6 (8.0%)
Moderate LV PGD	3 (4.0%)
RV PGD	2 (2.7%)
Primary Graft Failure Requiring Re-transplantation	1 (1.3%)

The safety endpoint (Table 46) was the average number of HGRSAEs experienced by TR recipients. Since each subject was at risk of experiencing a maximum of 4 HGRSAEs, the safety endpoint could have ranged from 0-4. One subject developed 2 HGRSAEs (severe LV PGD + re-transplantation).

Table 46: Safety Endpoint Results

Safety Endpoint Mean number of HGRSAEs	TR population (N=75)	95% CI of Proportion
Number of HGRSAEs	12	-
Subjects with a HGRSAE (n/N)	14.7% (11/75)	-
Mean number of HGRSAEs/subject (Safety Endpoint)	0.16 (12/75)	(0.1 – 0.2)

Serious Adverse Events

FDA found the types and rates of SAEs to be consistent with expectations for heart transplantation studies. A total of 75% of TR subjects experienced an SAE, and 41% experienced a cardiac SAE. Notable per subject SAE rates were stroke (4%), acute renal failure (13%), and allograft rejection events (16%). As with PROCEED II, no SAEs were adjudicated as having been device-related.

PROTOCOL DEVIATIONS

Protocol deviations were compiled by TransMedics (Table 47). Unlike PROCEED II, there was no sub-classification as "violation" versus "deviation." The majority of deviations were related to assessments performed out-of-window and thus are unlikely to have affected the results. However, FDA notes that there were no "Failure to follow IFU" deviations listed. This accounting is not accurate, as TransMedics informed FDA of 17 IFU deviations involving disconnection of the PA cannula.

Table 47: EXPAND Protocol Deviations

PROTOCOL DEVIATIONS
TRANSPLANTED RECIPIENT POPULATION

Type of Protocol Deviation	OCS (N=75) n (%)
Any Protocol Deviation	49 (65.3%)
Donor Eligibility Criteria	0
Donor assessment not performed	17 (22.7%)
Donor assessment out of time window	32 (42.7%)
Recipient eligibility criteria not met	0
Recipient assessment not performed	7 (9.3%)
Recipient assessment out of window	10 (13.3%)
Failure to follow IFU	0
Other	9 (12.0%)

7.3 EXPAND CAP

7.3.1 Study Design

EXPAND CAP (CAP) was a multicenter, single arm trial approved to preserve on the OCS Heart System and transplant up to 75 donor hearts not meeting sponsor-defined standard donor heart acceptance criteria. The study included a total of 10 sites identified by the sponsor.

INCLUSION AND EXCLUSION CRITERIA

Recipient inclusion and exclusion criteria for CAP were the same as EXPAND except for the following:

- EXPAND excluded all subjects with a diagnosis of "chronic renal insufficiency" (CRI), whereas CAP excluded patients with CRI requiring hemodialysis or renal replacement therapy.

Donor inclusion and exclusion criteria for CAP were similar to EXPAND except that CAP:

- Modified the timing and duration of the ejection fraction exclusion criterion datapoint;
- Clarified the definition of "significant coronary artery disease" as being <50% on angiogram;
- Clarified that a "history" of carbon monoxide (CO) poisoning, rather than death "caused by" CO was an inclusion.

FDA Comment: Prior to the request for a CAP study in October 2018, and the submission of the EXPAND PMA in December 2018, FDA observed that the most frequent reason for EXPAND donor hearts to be considered "expanded criteria" was expected cross-clamp time (ECCT) ≥ 4 hours, noting to the sponsor that this corresponded to a sizeable sub-group of EXPAND donor hearts structurally and functionally more analogous to standard-criteria donor hearts than the donor hearts included on the basis of the other listed expanded donor criteria. FDA cautioned that it was not possible to know *a priori* whether the collected data from EXPAND would, if favorable in aggregate, be applicable to all expanded donor criteria subgroups. To facilitate subsequent PMA determinations, FDA therefore suggested in August 2018 that the data from EXPAND inform a choice of a narrower donor heart population for the follow-on investigation. Specifically, FDA recommended that TransMedics consider limiting the requested supplemental study to donor hearts with ECCT ≥ 4 hours and/or reported down-time ≥ 20 minutes. The sponsor disagreed with this recommendation, and therefore FDA alternatively requested that the EXPAND CAP protocol be as consistent as possible with EXPAND, so that the CAP data might supplement the pivotal study's data. FDA indicated that an analysis of pooled data from EXPAND and EXPAND CAP (without hypothesis-testing) could assist in the overall assessment of the device's safety and effectiveness.

ENDPOINTS

CAP had a single Primary Endpoint of transplant recipient and allograft survival at post-operative day (POD) 30 in the absence of severe primary heart graft dysfunction (PGD) in the first 24 hours post-transplantation. This unpowered endpoint was the same as the powered, hypothesis-tested Primary Effectiveness Endpoint of EXPAND. CAP's three secondary endpoints and a single safety endpoint evaluating heart graft-related serious adverse events (SAEs) were the same as EXPAND. CAP defined 4 "other endpoints" (survival at 6 and 12 months, PGD leading to re-transplantation, duration of initial ICU stay, and duration of initial hospitalization); these data, while not specified as endpoints in EXPAND, were collected in the earlier study.

ANALYSIS POPULATIONS

CAP's two pre-specified analysis populations (TR for recipients, OCS-H for donor hearts) were the same as EXPAND's, except that, unlike in EXPAND, CAP's TR population did not exclude recipients for whom there were:

- donor or recipient inclusion/exclusion criteria violations;
- protocol violations; or
- IFU failures.

As noted in Section 7.2.2, FDA recommended that EXPAND include ITT and mITT analysis populations, but this was not done. In CAP, the sponsor further clarified that a subject (recipient) was enrolled only after transplantation with an OCS-instrumented donor organ; all other recipient-donor matches were considered "screen failures."

7.3.2 Study Enrollment

The study was approved for up to 8 sites, though a total of 10 sites were included by the sponsor. At the time of database lock (August 26, 2020), 50 recipients had consented, 3 had withdrawn (transplantation

off-study), and 2 remained on the waiting list. 45 subjects were enrolled after transplantation (TR population), but 4 of them (3 at Site C01 and 1 at Site C06) had not yet reached the 30-day post-transplantation Primary Endpoint time point and were censored from the TR analysis population.

Forty-nine (49) donor hearts were procured and instrumented onto the device. Four (4) of these OCS-H population donor hearts were turned-down by investigators after support.

Table 48: EXPAND CAP Sites

SITE	Site #	Transplanted (%) (n=41 with at least 30-day data)	Turned Down (n=4)
(b) (6)	C01	24 (59%) [+3 censored]	0
	C03	5 (12%)	0
	C04	0	2
	C05	4 (10%)	0
	C06	5 (12%) [+1 censored]	0
	C08	0	1
	C011	1 (2%)	0
	C012	2 (5%)	1
	C09	0	0
	C02	0	0

Four (4) of the 10 sites in EXPAND CAP also enrolled in EXPAND (C01, C06, C02, and C011), in which they were middle-to-high-enrolling centers. 2 sites were newly activated for CAP (C03 and C08), while 3 sites, although previously activated for EXPAND, did not enroll EXPAND subjects(C04, C05, and C012). One site (C09) activated for CAP did not contribute any donors or recipients.

FDA Comment: A single site (C01 (b) (6)) enrolled a majority of the subjects in CAP. This site was also the highest enrolling site in EXPAND. FDA repeatedly advised the sponsor that such subject distribution was not consistent with the intent of either the CAP or the IDE trial and introduced challenges to data interpretability and generalizability.

EXPAND sites that were selected to participate in EXPAND CAP had higher subject survival and donor heart utilization rates vs. EXPAND sites that were not invited to participate in EXPAND CAP (Table 49):

Table 49: EXPAND Clinical Sites included as EXPAND CAP Clinical Sites

EXPAND Site	EXPAND Enrollment (N)	1-year Survival Rate n/N (%)	Utilization rate N/X* (%)
EXPAND Sites included as EXPAND CAP Sites			
(b) (6) (site #6)	29	26/29 (90%)	29/34 (85%)
(b) (6) (site #11)	3	3/3 (100%)	3/4 (75%)
(b) (6) (site #3)	13	12/13 (92%) *Subject (b) (6) was enrolled, withdrawn on POD 6, re-transplanted on day 7*	13/16 (81%)
(b) (6) (site #9)	7	7/7 (100%)	7/10 (70%)
AVERAGE		**92%**	**81%**
EXPAND Sites excluded from EXPAND CAP			
(b) (6) (site #4)	1	0/1 (0%)	1/2 (50%)
(b) (6) (site #5)	2	1/2 (50%)	2/5 (40%)
(b) (6) (site #10)	12	7/12 (58%)	12/14 (86%)
(b) (6)	1	1/1 (100%)	1/1 (100%)
AVERAGE		**56%**	**73%**

* X=number of donor hearts supported by the OCS Heart System

7.3.3 Donor Heart Demographics and Characteristics

Pre-procurement Demographics

Key donor and recipient demographic and baseline characteristics for the TR population are presented in Table 50. Compared to EXPAND, although there were proportionately fewer female donors (28% EXPAND vs. 15% CAP), the female-to-male donor mismatch rate was greater in EXPAND (16% EXPAND vs. 0% CAP, p=0.01). The following trends were also noted:

- Pre-transplantation VAD use was substantially lower in CAP, while pre-transplantation IABP use was more frequent, perhaps reflecting UNOS wait-list modifications that now prioritize IABP use over VAD support. A higher proportion of CAP recipients were UNOS Status II (Status 6).
- CAP recipients trended toward being younger and included a higher proportion of Blacks. The age of CAP donors was similar to EXPAND and included a lower proportion of Blacks.

- CAP recipients had less pre-existing chronic renal dysfunction (although the renal dysfunction definitions differed).

Table 50: CAP Transplant Recipient and Donor (pre-procurement) Baseline Characteristics

Baseline Characteristics				
		Recipients (n=41)		**Donors (n=41)**
Age				
	Mean (SD)	52.13 (14.21)		36.65 (10.34)
	Median	56.40		36.50
	Min - Max	19.4 – 69.9		18.9 – 56.2
Gender				
Male	n (%)	32 (78.0)		35 (85.4)
Female	n (%)	9 (22.0)		6 (14.6)
Race				
American Indian or Alaskan Native	n (%)	0		0
Asian	n (%)	0		1 (2.4)
Black of African American	n (%)	12 (29.3)		6 (14.6)
White	n (%)	28 (68.3)		28 (68.3)
Other	n (%)	1 (2.4)		2 (4.9)
Unknown	N	0		4 (9.8)
BMI (kg/m2)				
	Mean (SD)	29.43 (4.68)		29.50 (8.61)
	Median	28.82		28.01
	Min - Max	19.7 – 39.4		19.0 – 49.6
Renal Dysfunction	N	41		
Yes	n (%)	1 (2.4)		-
No	n (%)	40 (97.6)		-
Donor Final Ejection Fraction (%)	N	-		41
	Mean (SD)	-		59.7 (7.83)
	Median	-		60.0

	Min - Max	-		45 - 78
Recipient Panel Reactive Antibody (%)	N	41		-
	Mean (SD)	6.6 (17.90)		-
	Median	0.0		-
	Min - Max	0 - 79		-
Recipient Listing Status	N	41		-
IA (Status 1-3)	n (%)	25 (61.0%)		-
IB (Status 4)	n (%)	12 (29.3%)		-
II (Status 6)	n (%)	4 (9.8%)		-
Male recipient/Female donor	N	32		6
Female donor to male recipient	n (%)	0		0
Recipient MCS	N	41		-
IABP	n (%)	16 (39.0%)		-
LVAD	n (%)	11 (26.8%)		-
RVAD	n (%)	1 (2.4%)		-
BiVAD	n (%)	0		
ECMO	n (%)	2 (4.9%)		

7.3.4 Donor Heart Inclusion Criteria

Donor organs were accepted into the study if they fulfilled one or more inclusion criteria. The distribution of qualifying criteria for the OCS-H population (hearts perfused with the OCS Heart System) is shown in Table 51. 28/45 (62%) of OCS-H hearts were included on the basis of a single inclusion criterion; expected cross-clamp time ≥ 4 hours (ECCT ≥ 4) accounted for 19 of the 28 (68%) single-criterion donor organs, making anticipated cross-clamp time alone the most frequent reason investigators opted for the device (42% of the CAP procurements). As noted in Section 7.2.5, single-criterion ECCT ≥ 4 hours was also the most common reason for EXPAND investigators to use the device; 21/93 (23%) EXPAND procurements were based on this criterion alone.

Four (4) OCS-H hearts (9%) were turned-down after perfusion with the device (Table 51). All four were single-criterion ECCT ≥ 4 hours, which corresponds to 21% (4/19) of CAP ECCT ≥ 4 hour-only hearts turned-down after initial acceptance and procurement. In EXPAND (Section 7.2.5), 14% of ECCT ≥ 4-only hearts were turned-down after initial acceptance and procurement.

Table 51: CAP Donor Heart Inclusion Criteria

Donor inclusion criteria OCS-H hearts (n=45)	TR hearts (n=41)	Turned-down hearts (n=4)
Single criterion	24	4
Multiple criteria	17	0
ECCT ≥ 4	25	4
Downtime ≥ 20 min	10	-
EtOH	7	-
EF ≥ 40% ≤ 50%	6	-
LVH	5	-
Luminal irregularities	3	-
≥ 55 y/o	2	-
CO as cause of death	0	-
Diabetes	1	-
45-55 y/o, no cardiac cath	0	-

Six (6) OCS-H donor hearts included "*LVEF ≥ 40%, but ≤ 50% at time of acceptance of* offer" as an inclusion criterion. However, FDA noted that 3 of these 6 hearts had subsequent pre-procurement LVEFs > 50%. In addition, 1 of these 6 hearts had an LVEF reported by UNOS as 50% based on an ECHO ((b) (6)), but an LVEF reported in the CRF of 60% based on an Angiogram ((b) (6)), 1 had an LVEF reported by UNOS as 55% (based upon echo report of "50-55%"), and 1 had serial echo's documenting EF=50-55% before a final echo reported EF=45-50%.

7.3.5 Donor Heart Preservation Summary

Preservation Parameters

OCS Heart perfusion parameters are shown in Table 52. Ischemic and pump perfusion times for transplanted donor hearts were similar in CAP and EXPAND (average OCS perfusion time ~4½ hours, average ischemic time ~1¾ hours). Turned-down donor hearts had similar pre-OCS ischemic times EXPAND vs CAP (~30 minutes), but modestly longer OCS perfusion times as compared to the corresponding transplanted population (an additional 20 minutes in EXPAND vs. 50 minutes in CAP).

Perfusion parameters (aortic pressure (AOP) and coronary flow) were clinically similar across the two studies, and there were no clinically evident differences between OCS-H organs that were transplanted and those that were turned-down in CAP or EXPAND. Average initial and final lactate levels in CAP were similar to EXPAND, although the range of what final lactate levels investigators considered to be acceptable for transplantation was wider in CAP. There were 4 CAP OCS-H donor organs that had a final arterial lactate > 5.0 mmol/L, 2 of which were transplanted, and 2 of which were turned-down after perfusion (Table 53). One of the transplanted hearts ((b) (6)) had a pre-instrumentation arterial lactate of 5.25 mmol/L.

Table 52: Preservation Parameters CAP

OCS-H Population Preservation Parameters		TR hearts (N=41)	Turned-down hearts (N=4)
Pre-OCS Ischemic Time (mins)	n	41	4
	Mean (SD)	37.2 (17.1)	29.8 (5.9)
	Median	33	30.5
	Min - Max	20 - 99	22 - 36
OCS Perfusion Time (mins)	n	41	4
	Mean (SD)	278.3 (77.2)	328.5 (56.5)
	Median	278	333
	Min - Max	158 - 440	256 - 392
Post-OCS Ischemic Time (mins)	n	41	n/a
	Mean (SD)	66.7 (14.9)	
	Median	66	
	Min - Max	20 - 105	
Total Ischemic Time (mins)	n	41	n/a
	Mean (SD)	104.0 (22.2)	
	Median	98	
	Min - Max	69 - 189	
Total "Cross Clamp" Time (min)	n	41	n/a
	Mean (SD)	382.3 (87.9)	
	Median	385.0	
	Min - Max	253 - 585	
Arterial Lactate—Initial OCS	n	41	4
	Mean (SD)	1.8 (0.85)	2.2 (1.04)
	Median	1.7	1.9
	Min - Max	0.67 – 5.70	1.29 – 3.69
Arterial Lactate—Final OCS	n	41	4
	Mean (SD)	2.9 (1.26)	5.7 (1.74)
	Median	2.6	5.5
	Min - Max	1.28 - 7.59	3.92 – 7.89
AOP Mean (mmHg)	n	41	4
	Mean (SD)	77.4 (8.5)	77.3 (12.7)
	Median	79.3	80.9
	Min - Max	52 - 96	59 - 88
Coronary Flow (L/min)	n	41	4
	Mean (SD)	0.729 (0.113)	0.710 (0.178)
	Median	0.750	0.791
	Min - Max	0.32 – 0.92	0.44 - 0.81

Table 53: EXPAND CAP Hearts with a Final Arterial Lactate > 5 mmol/L

Site	Subject	UNOS ID	Final Lactate (mmol/L)	Outcome
(b) (6)	(b) (6)	(b) (6)	6.3	Tx
			7.59	Tx
			7.89	TD
			6.27	TD

TD = Turned down heart; Tx = transplanted heart

PA Cannula Disconnections

Based upon the OCS coronary flow trend data, FDA identified 5/45 (11%) CAP OCS-H donor organs for which the PA outflow cannula was disconnected during some of the perfusion period. In EXPAND, PA cannular disconnection occurred in 18% of OCS-H organs (performed to address perceived donor heart RV dysfunction on the device). One of the 5 CAP hearts with PA outflow cannula disconnection was subsequently turned-down after preservation, and 2 of the 4 transplanted CAP hearts with PA outflow cannula disconnection had final lactate levels > 5.0 mmol/L.

7.3.6 EXPAND CAP Study Results

CAP Primary, Secondary, and Safety Endpoints results were similar to those observed in EXPAND.

Effectiveness Results

Primary Endpoint

Table 54: Primary Endpoint

Survival at POD 30 without severe PGD (LV or RV)	TR population (N=41)	95% CI of Proportion
Proportion (n/N)	97.6% (40/41)	87.1 – 99.9

Secondary Endpoints

Table 55: Patient and Graft Survival at Day 30 Post-transplantation

Patient/Graft Survival at POD 30	TR population (N=41)	95% CI of Proportion
Proportion (n/N)	100% (41/41)	91.4 - 100

Table 56: Incidence of severe PGD in the first 24 hours post-transplantation

Incidence of Severe PGD (LV or RV)	TR population (N=41)	95% CI of Proportion
Proportion (n/N)	2.4% (1/41)	0.1-12.9

Table 57: Donor heart utilization

Donor Heart Utilization	OCS-H population (N=45)
Proportion (n/N)	91% (41/45)

Safety Results

Safety Endpoint

The safety endpoint was based upon the occurrence of HGRSAEs (Table 58).

Table 58: Heart Graft-Related SAEs

PRIMARY SAFETY ENDPOINT AND LISTING OF HGRSAES BY TYPE
OCS TRANSPLANTED RECIPIENTS POPULATION

Parameter	Statistic	OCS (N=41)
Number of heart graft-related serious adverse events up to 30 days after transplantation	n	41
	Mean	0.2
	Median	0.0
	SD	0.38
	Minimum - Maximum	0 - 1
	95% CI for Mean (1)	(0.1, 0.3)
HGRSAEs by Type		
Moderate or severe PGD (LV or RV), n/N (%)	n/N (%)	7/41 (17.1%)
Primary Graft Failure requiring re-transplantation	n/N (%)	0

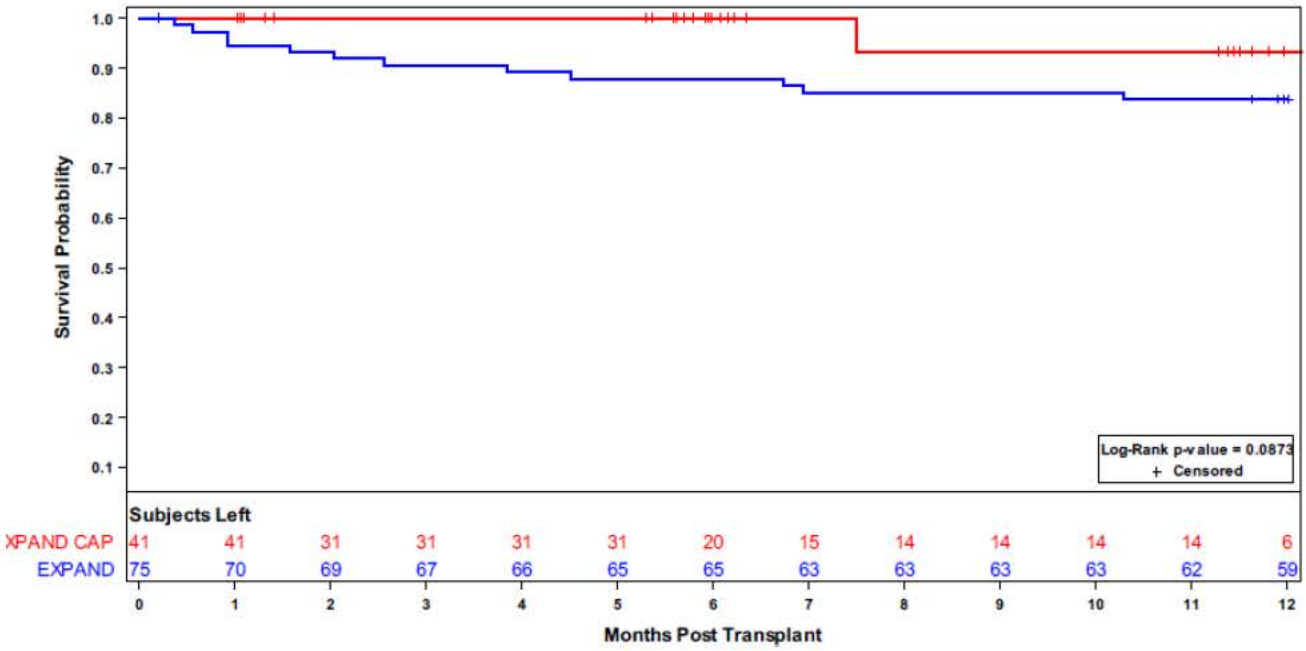
Table 59: Safety Endpoint Results

Safety Endpoint Mean number of HGRSAEs	TR population (N=41)	95% CI of Proportion
Number of HGRSAEs	7	-
Subjects with a HGRSAE (n/N)	17.1% (7/41)	-
Mean number of HGRSAEs/subject (Safety Endpoint)	0.2 (7/41)	(0.1 – 0.3)

Longer-term Survival

Six and 12-month survival analysis were pre-specified in the CAP protocol for the TR population. Six and 12-month survival probabilities were 100% and 93%, respectively. In EXPAND, the survival probabilities were 93% and 84% at 6 and 12 months, respectively (Figure 18).

Figure 18 EXPAND and EXPAND CAP 6-Month and 12-Month Survival Probabilities



Of note, the CAP survival curve includes a substantial amount of censoring due to many of the 41 TR subjects not having reached the follow-up time points: 21/41 (51%) censored prior to 6 months, and 34/41 (83%) censored prior to 12 months.

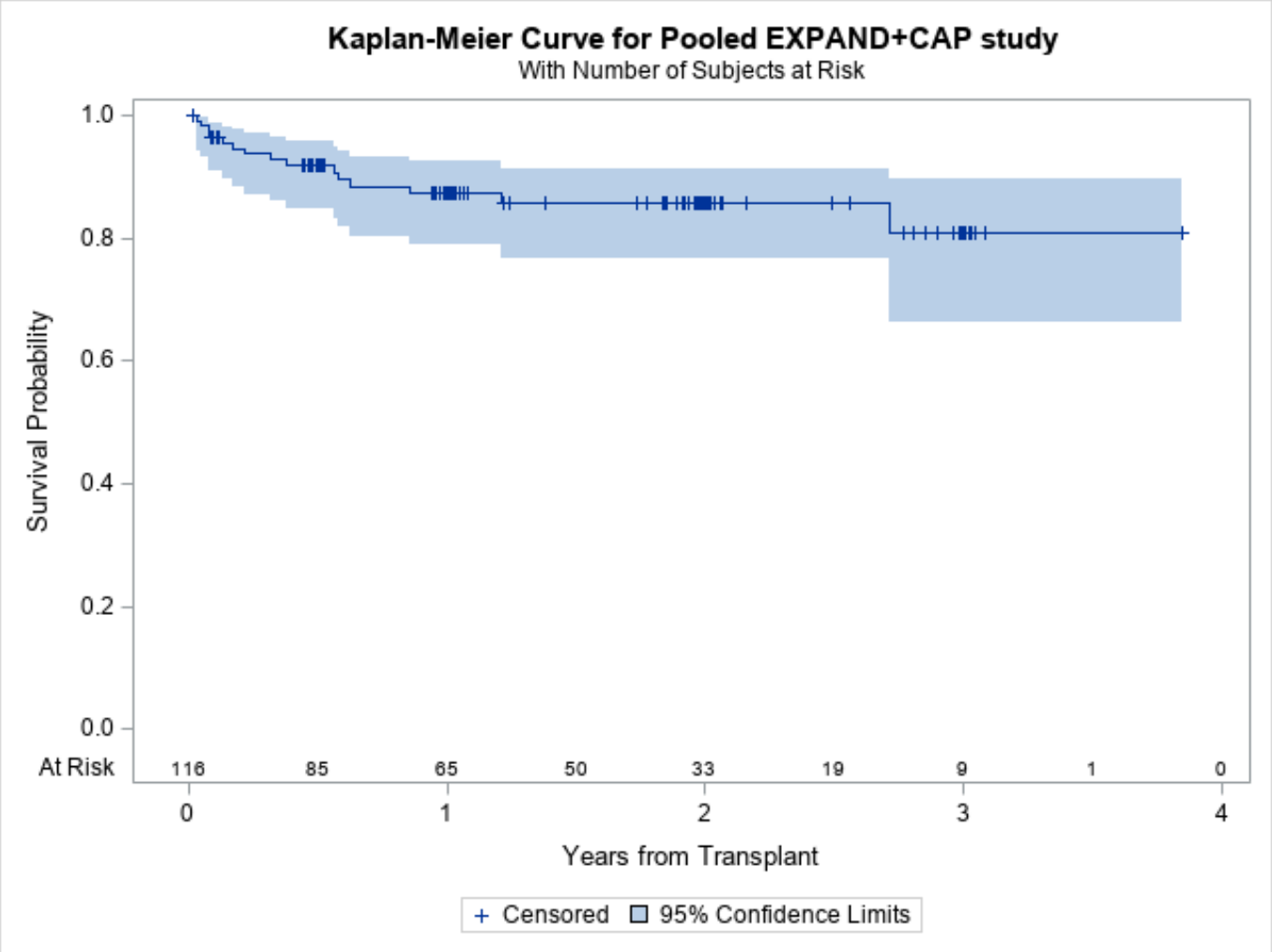
POOLED EXPAND AND EXPAND CAP KAPLAN-MEIER CURVES AND FITTED PARAMETRIC MODELS

Kaplan-Meier Curve

Enrollment criteria and endpoints were generally the same for CAP and EXPAND. Notwithstanding site disparity and demographic baseline characteristic differences between CAP and EXPAND donors and recipients, FDA believes the two datasets are poolable from a clinical standpoint.

A Kaplan-Meier survival analysis for Pooled EXPAND and EXPAND CAP is shown in Figure 19 demonstrating survival rates of 87.2% at 1-year, 85.5% at 2 years, and 80.8% at 3-years.

Figure 19 Kaplan-Meier Curve for Pooled EXPAND and EXPAND CAP

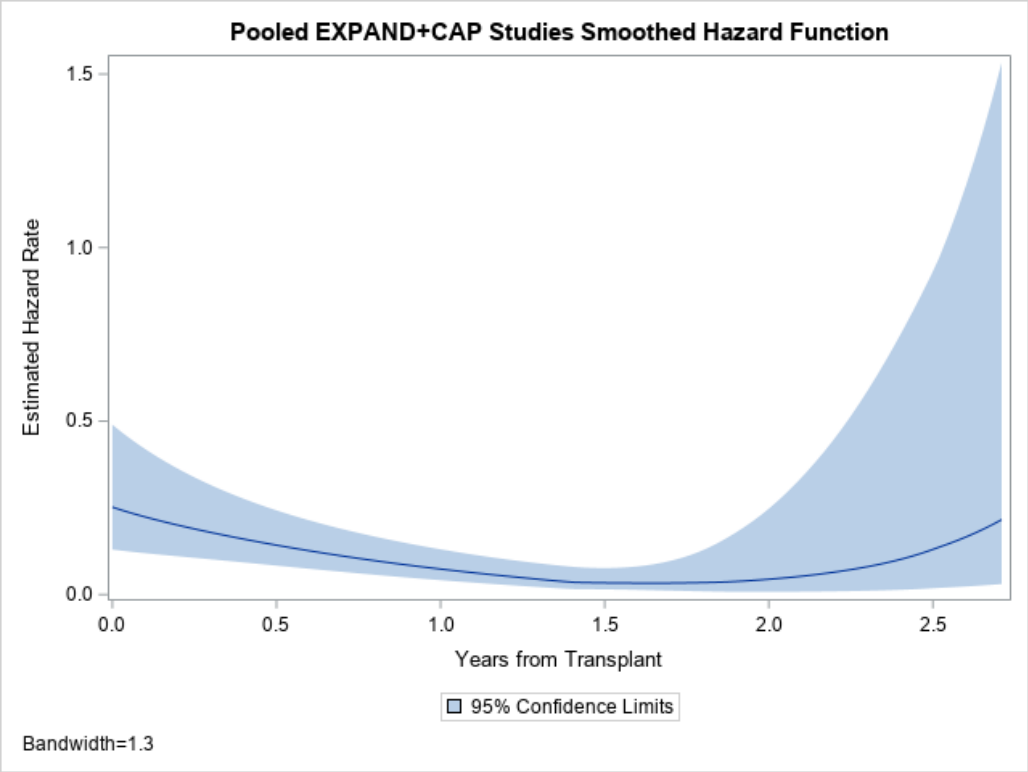


Fitted Parametric Models

To estimate the longer-term survival rates, we applied various parametric models (analogous to the parametric modeling method described earlier) to extrapolate to longer-term survival rates from the pooled available EXPAND + EXPAND CAP data.

From the Kernel-Smoothed Hazard Function plot in Figure 20, it appears that the hazard function tends to decrease early post-heart transplantation and then increase. The variance of the estimated hazard rate tends to increase towards the end of the follow-up when fewer patients are at risk.

Figure 20: Pooled EXPAND and EXPAND CAP Smoothed Hazard Function



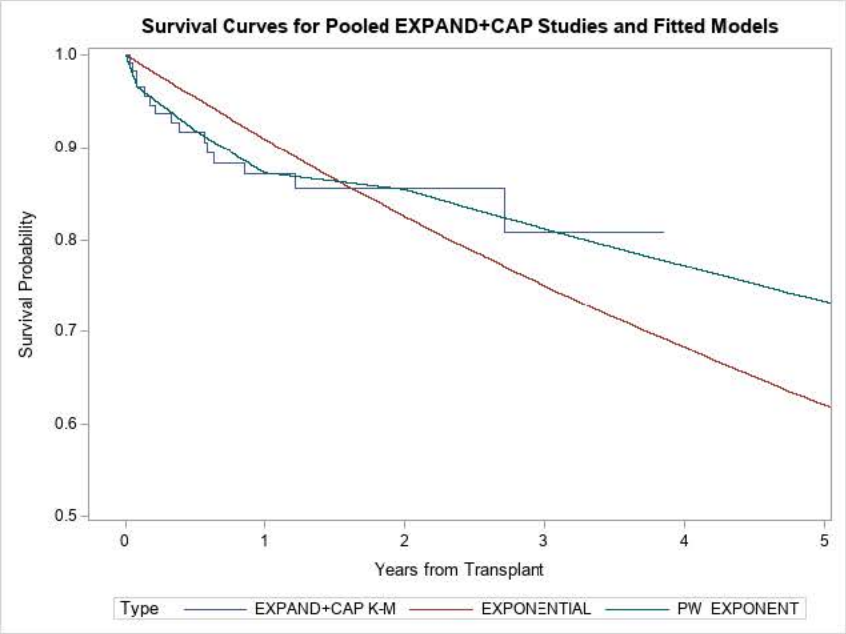
Similar to the PROCEED II and EXPAND analyses, FDA applied exponential and piece-wise models to pooled EXPAND and EXPAND CAP data to extrapolate the survival function. For the piece-wise exponential model, FDA specified the following intervals: 0 to 30 days, (30 to 180days, 180 to 365days, 365 to 730days, and > 730 days. Table 60 shows the estimated survival rates and confidence intervals using the two parametric models and survival rates estimated by Kaplan-Meier. Figure 21 shows the pooled EXPAND and EXPAND CAP Study (EXPAND+CAP) Kaplan-Meier survival curve and the survival functions of the fitted parametric models.

Table 60: Survival Probability of the Pooled EXPAND and EXPAND CAP Dataset

Time Post-transplantation	Survival Probability % (95% CI)		
	Exponential Model*	Piecewise Model*	Kaplan-Meier
1 Year	90.9 (85.4, 94.4)	87.1 (79.9, 92.9)	87.2 (78.8, 92.4)
2 Years	82.7 (72.9, 89.2)	85.4 (77.6, 91.7)	85.5 (76.5, 91.3)
3 Years	75.2 (62.3, 84.2)	81.1 (69.4, 89.7)	80.8 (66.3, 89.5)
4 Years	68.3 (53.2, 79.5)	77.1 (58.3, 88.8)	-
5 Years	62.1 (45.4, 75.0)	73.2 (48.8, 88.2)	-

*Fitted exponential model parameter is $\lambda = 0.0002\,6095$. Fitted piecewise exponential model parameters are $\lambda = 0.00117$ (0-30days), 0.000341 (30-180days), 0.000281 180-365days), 0.000055 (365-730days), 0.000140 (730-∞).

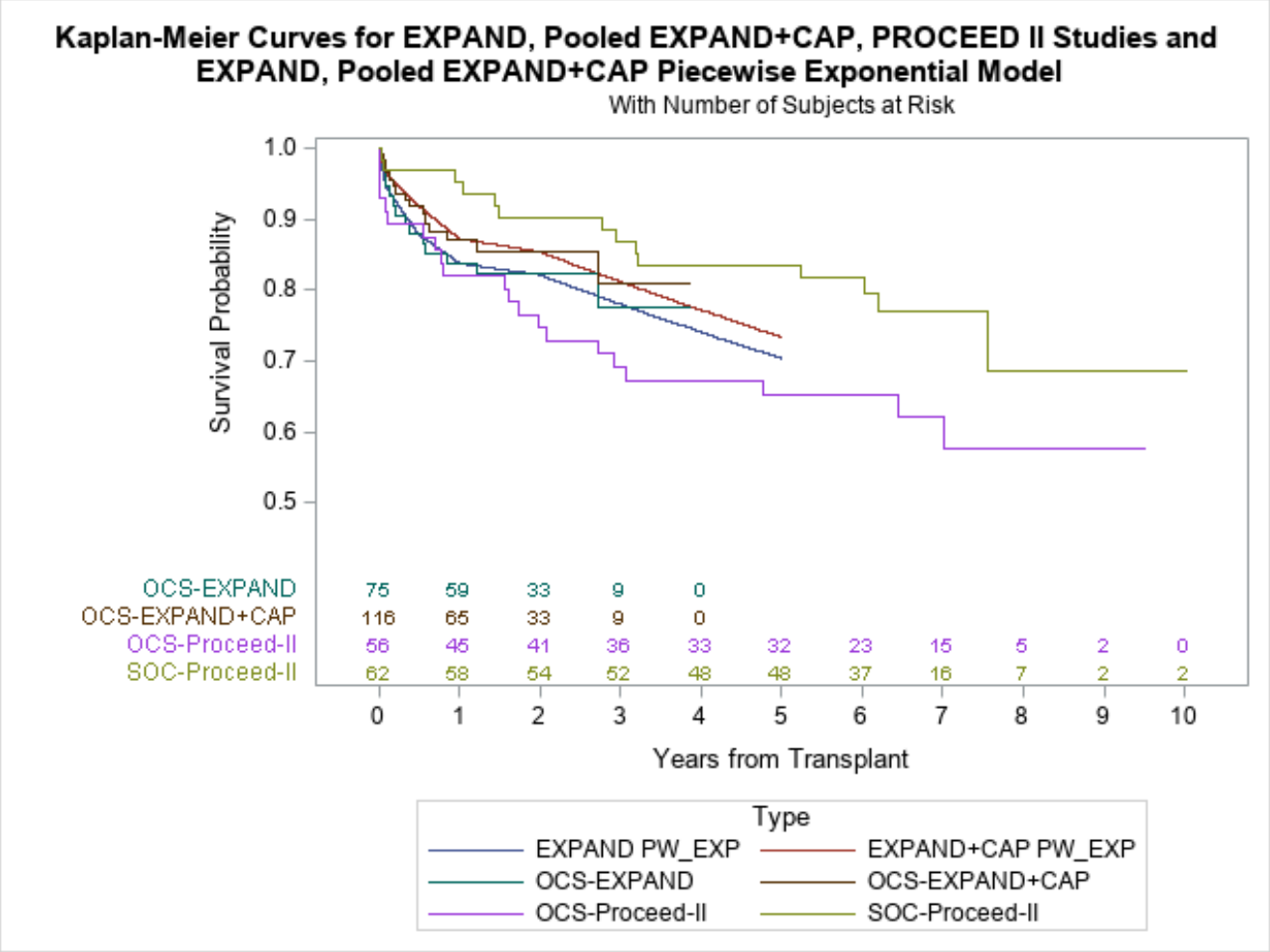
Figure 21: Survival Curves for the Pooled EXPAND + CAP Data Set and Fitted Models



EXPAND+CAP K-M: Pooled EXPAND+CAP Studies Kaplan-Meier Curve
EXPONENTIAL: The Fitted Exponential Model
PW_EXPONENT: The Fitted Piece-Wise Exponential Model

According to the estimated hazard function, the piece-wise exponential model appears to be a more reasonable choice than the exponential model for the pooled EXPAND and EXPAND CAP dataset, because the estimated hazard function does not seem to be a constant. Figure 22 shows a combined plot that includes Kaplan-Meier curves for PROCEED II, EXPAND, and the pooled EXPAND+CAP dataset, with a prediction for the EXPAND and EXPAND+CAP pooled dataset.

Figure 22: Kaplan-Meier Curves for EXPAND, Pooled EXPAND+CAP, Proceed II and EXPAND, and Pooled EXPAND+CAP Piecewise Exponential Model



As shown in Figure 22, pooling of CAP with EXPAND shifts the extended-criteria heart survival curve upward. However, due to the large variability in KM estimates (presented in Table 60), the high proportion of CAP subjects enrolled at a single site, and limitations associated with comparing results across different studies, this observation should be interpreted with caution.

Post-hoc Analyses of Donor Heart Inclusion Criteria in Pooled EXPAND+CAP

Single-criterion ECCT ≥ 4 hours was the most frequent justification for use of the device in EXPAND, and this pattern was observed in CAP. Single-criterion ECCT ≥ 4 hours accounted for 29% (40/138) of the pooled OCS-H population (Table 63) and 28% (33/116) of the pooled TR population (Table 61). Forty-eight percent (48%) of EXPAND+CAP organs were prospectively identified as having ECCT ≥ 4 hours (29% as the sole inclusion criterion, 19% with other criteria).

Table 61: Donor Inclusion Criteria by Study – Transplanted Hearts (TR)

	EXPAND (N=75)	CAP (N=41)	EXP (updated)+CAP (N=116)
ECCT≥4 hrs (as a criterion)	28/75 (37%)	25/41 (61%)	53/116 (46%)
ECCT≥4 hrs (sole criterion)	18/75 (24%)	15/41 (37%)	33/116 (28%)

Table 62: Donor Inclusion Criteria by Study – Turned Down Hearts

	EXPAND (N=18)	CAP (N=4)	EXP (updated)+CAP (N=22)
ECCT≥4 hrs (as a criterion)	9/18 (50%)	4/4 (100%)	13/22 (59%)
ECCT≥4 hrs (sole criterion)	3/18 (17%)	4/4 (100%)	7/22 (32%)

Table 63: Donor Inclusion Criteria OCS-H Population EXPAND+CAP

	OCS-H Population EXPAND+CAP (N=138)
ECCT≥4 hrs (as a criterion)	66/138 (48%)
ECCT≥4 hrs (sole criterion)	40/138 (29%)

Eighteen percent (7/40) of the EXPAND+CAP OCS-H organs with ECCT ≥ 4 hours as the sole inclusion criterion were turned-down for transplantation after device preservation. 15/98 (15%) of the other EXPAND+CAP OCS-preserved hearts were turned-down.

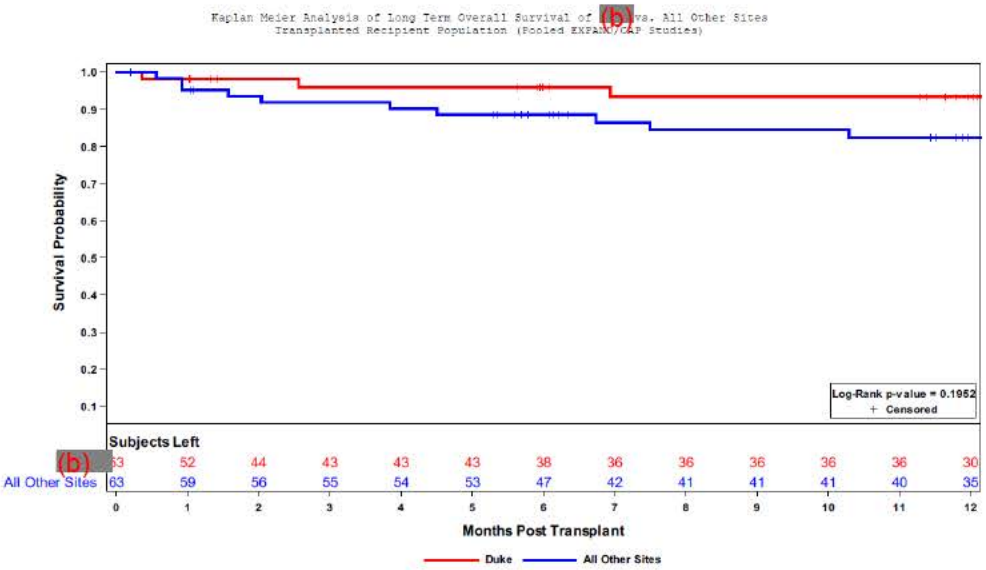
12-month survival in EXPAND for transplanted hearts with the single-criterion ECCT ≥ 4 hours was 88% (see Figure I.6 in Appendix I). 9% (3/33) of EXPAND+CAP subjects transplanted with single-criterion ECCT ≥ 4 hours have died within one year, accounting for 23% (3/13) of all 12-month deaths thus far (follow-up not yet complete).

FDA Comment: FDA believes a donor heart meeting only the inclusion criterion ECCT ≥ 4 hours was, at the time of procurement, functionally and clinically analogous to a standard-criteria donor organ. Although the OCS device is specifically designed to offset deleterious effects of prolonged cold ischemia (i.e., > 4 hours), *post hoc* analyses indicate that the turn-down rate (18%) among these "functionally" standard-criteria donor organs after > 4 hours of machine preservation was relatively high, in contrast to both the SRTR database (< 1%) and to the results from standard-criteria hearts in PROCEED II (0% SOC, 7% OCS). One-year survival in this subgroup of donor hearts after OCS preservation is below that of standard-criteria donor hearts procured and transported with cold static preservation techniques. Considering the totality of data, the Panel will be asked to discuss any concerns regarding device use on the basis of anticipated cross-clamp time absent other co-existing extended donor characteristics. The Panel will also be asked to consider the proposed Indications for Use and labeling and whether modifications are needed to ensure a reasonable assurance of safety and effectiveness regarding extended donor characteristics.

Longer-term Survival – Site Effect

A site effect analysis for the Primary Endpoint found no adjustments were needed for site effects for the pooled dataset (p=0.8818). 53/116 (43%) pooled TR subjects were from the high-enrolling site (C01, (b) (6)). FDA requested a *post hoc* analysis of survival comparing (b) to all other sites. The 12-month survival at (b) (6) was 93% (95% CI: 80, 98), and the survival estimate at the other sites combined was 82% (95% CI: 69, 90).

Figure 24: Survival of (b) (6) vs. All Other Sites



Of note, 8 of (b) (6) 58 OCS-H donor hearts (14%) were single-criterion ECCT ≥ 4 hours; 32 of the combined other sites' 80 OCS-H hearts (40%) were that sole criterion.

8. Turned-Down Hearts: Clinical and Clinicopathologic Analyses

8.1 PROCEED II Turned-Down Donor Hearts: Clinical Analysis

Five (5) PROCEED II OCS Heart System-preserved donor hearts (for 4 recipients) were turned down by investigators after preservation with the device and not transplanted. The reason for turn-down was rising lactate for 3 hearts, inability to maintain aortic cannula positioning in 1, and aortic regurgitation in 1. Two of the 4 enrolled recipients were transplanted off-study (1 screen failure, 1 withdrawal). The other 2 patients maintained their randomization assignment with subsequent waiting list periods of 2 and 6 weeks.

Lactate level was the cited clinical reason for turn-down of 3 hearts. Elevated lactate immediately prior to donor cardiectomy was also the justification for one surgeon's decision to preserve an OCS Heart-randomized subject's donor organ ((b) (6)) with SOC instead. Rising lactate level was observed during the course of OCS Heart support in 4 of the 5 turned down hearts. Starting *in vivo* lactate levels were clinically similar for transplanted and turned-down OCS Heart supported hearts (Figure 18). No blood lactate data were obtained from SOC-randomized donor organs during the harvesting procedure.

Figure 25: Lactate levels for transplanted and turned-down OCS Hearts (PROCEED II)

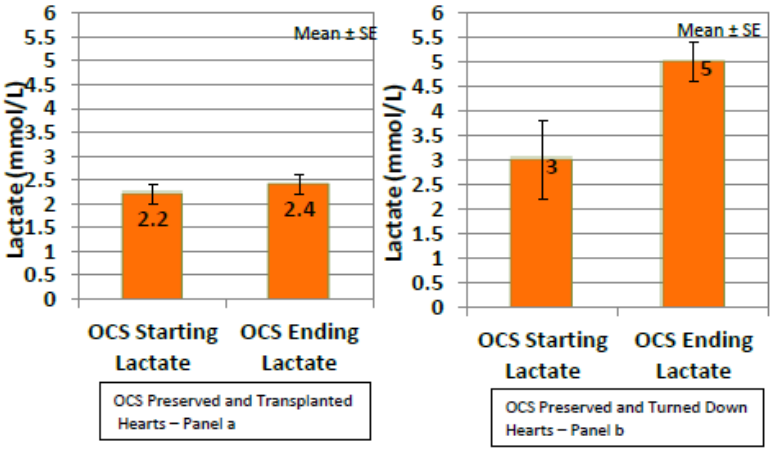


Figure 3-1: Starting and Ending Levels for OCS Preserved Hearts That Were Transplanted (Panel a) versus OCS Preserved Hearts That Were Turned Down for Transplantation (Panel b)

Among the 4 OCS Heart recipients who failed the Primary Study Endpoint, rising lactate while on OCS Heart perfusion was not a reproducible finding; average lactate at the end of OCS Heart perfusion in these patients was unchanged from the average starting value (2.4 mmol/L).

The sponsor explained that the turned-down hearts had "undiagnosed pre-retrieval pathologies that render these hearts to be considered 'non-standard' and represent potential high risk to patients." Given the randomized trial design, FDA believes a similar incidence of non-standard donor hearts would likely have

been present in the SOC control arm. In an independent analysis, FDA reviewed the core pathologist's reports (see Appendix E) for each of the turned down hearts. FDA does not support the *post facto* conclusion that the turned-down hearts were probably unsuitable for transplantation because of pre-existing pathologies. See FDA's pathologic analysis of turned-down hearts below for further discussion. Of note, turn-down of conventionally preserved donor hearts is a very rare occurrence in clinical practice but represented 7% of accepted PROCEED II standard-criteria OCS Heart perfused hearts.

For randomized subjects who were not transplanted with the initial heart but were transplanted with a second (or third) study organ, the protocol required separate reporting of adverse events (AEs) from the beginning of subject preparation for transplantation with the initial heart to the beginning of subject preparation for transplantation with subsequent hearts. Source documentation for Subjects (b) (6) and (b) (6) indicates the decisions to reject the donor organs were made after the subjects had been anesthetized, and Subject (b) (6) had had median sternotomy performed. Relevant source documents for the other 2 subjects (Subjects (b) (6) and (b) (6)) were not provided to FDA.

8.2 EXPAND Turned-Down Donor Hearts: Clinical Analysis

Turned-down donor hearts in EXPAND comprised 19% (18/93) of the OCS Heart donor population. The protocol-specified clinical criteria for donor heart transplantation at the conclusion of the support period with the OCS Heart device were as follows:

- final total arterial circulating OCS Heart perfusate lactate < 5 mmol/L
- stability of OCS Heart Perfusion Parameters within ranges:
  - mean AOP: 40-100 mmHg
  - CF: 400-900 ml/min

  LVH hearts may require higher CF and/or AOP

Among the turned-down hearts, investigators cited the following in the CRFs as qualifying criteria for preservation with the device (proportions differ from those in the amended dataset):

- ECCT ≥ 4 (n=6, 33%)
- EF ≥ 40% ≤ 50% (n=3, 17%)
- ECCT ≥ 4 + downtime ≥ 20 minutes (n=3, 17%)
- ECCT ≥2 + downtime ≥ 20 minutes (n=2, 11%)
- ECCT ≥2 + downtime ≥ 20 minutes + luminal irregularities/no CAD (n=1, 6%)
- ECCT ≥2 + downtime ≥ 20 minutes + luminal irregularities/no CAD + ≥ 55 y/o (n=1, 6%)
- ECCT ≥2 + luminal irregularities/no CAD (n=1, 6%)
- ECCT ≥2 + age 45-55, no cardiac catheterization (n=1, 6%)

Donor hearts: There were 18 EXPAND donor hearts placed on the OCS Heart System and intended for transplant but were subsequently deemed unsuitable for use. Donor hearts were from 15 men and 3 women (mean age 31 ± 15 years, range 13 to 56 years). Brain death was due to intracranial bleeding in

5 cases, asphyxia/suicide in 4 cases, drug overdose in 4 cases, head trauma in 4 cases, and drowning in 1 case. The study revised inclusion criteria met by the donor hearts are shown in Table 48.

Table 64: Inclusion criteria (revised) met by 18 EXPAND study turned down hearts

Inclusion Criteria	Number of hearts
Expected cross clamp time >4 hrs	3 hearts
Expected cross clamp time >4 hrs, plus down time	5 hearts
Expected cross clamp time >4 hrs, plus coronary luminal irregularities	1 heart
Expected cross clamp time >2 hrs with:	
- Coronary luminal irregularities	1 hearts
- LVEF 40%	1 heart
- Down time and LVH	1 heart
- Down time and diabetes	1 heart
- LVEF 40% and history of alcohol abuse	1 heart
- Age 45-55	1 heart
- Age > 55, down time, and coronary luminal irregularities	1 heart
- Down time, and LVEF 45-50%	1 heart
- Down time, and luminal irregularities	1 heart

Donor heart echocardiogram assessment: Transthoracic echocardiography performed a mean of 1.5 ± 0.5 days (range 1 – 2 days) prior to donor heart removal showed a mean LV ejection fraction of 56 ± 11% (≥55% in 12 hearts, <50% in 4 hearts, and data not provided for 2 hearts). Echocardiograms showed no other significant cardiac structural abnormalities.

In the 18 turned-down hearts, the mean time from cross-clamp to the start of donor heart perfusion on the OCS Heart System was 31 ± 7 minutes (range 19 to 56 minutes), and the mean total OCS Heart System perfusion time was 299 ± 76 minutes (range 220 to 500 minutes). The mean aortic pressure and coronary flow rate were 83.2 ± 6.9 mm Hg (range 67.9 to 97.6 mm Hg) and 805 ± 45 ml/min (range 708 to 882 ml/min), respectively. Coronary flow data were excluded from 7 hearts in which the pulmonary artery catheter was disconnected for some time during heart perfusion. The mean final lactate level was 5.07 ± 0.82 mmol/L (range 3.50 to 7.17 mmol/L).

Besides "rising lactate" or "lactate trends," in most cases, no specific information was provided to explain the reasons why the transplanting surgeon/heart failure cardiologist was unsatisfied with donor heart evaluation on OCS Heart System.

For donor hearts *transplanted* in the EXPAND study (n=75), the mean time from cross-clamp to the start of donor heart perfusion on the OCS Heart System was 30 ± 8 minutes (range 15 to 53 minutes), the mean total OCS Heart System perfusion time was 279 ± 83 minutes (range 100 to 532 minutes), and the mean post-perfusion time was 72 ± 22 minutes (range 36 to 135 minutes). The mean aortic pressure and coronary flow rate was 80.8 ± 8.0 mm Hg (range 48.1 to 101.9) and 786 ± 54 ml/min (range 669 to 986 ml/min) respectively. Coronary flow data were excluded from 10 transplanted hearts in which the

pulmonary artery cannula was disconnected for some time during heart perfusion. The mean final lactate level was 3.09 ± 0.94 mmol/L (range 0.55 to 4.97 mmol/L).

A comparison of OCS Heart System perfusion parameters for donor hearts turned down for transplant vs. transplanted donor hearts is shown in Table 49. The OCS Heart System perfusion measures were generally similar between turn-down donor hearts and transplanted hearts except for a higher mean maximal lactate level in the turned down hearts (5.09 ± 0.81 vs. 3.09 ± 0.94 mmol/L, respectively).

Table 65: OCS Heart System perfusion parameters comparison between EXPAND donor hearts turned down for transplant and transplanted donor hearts

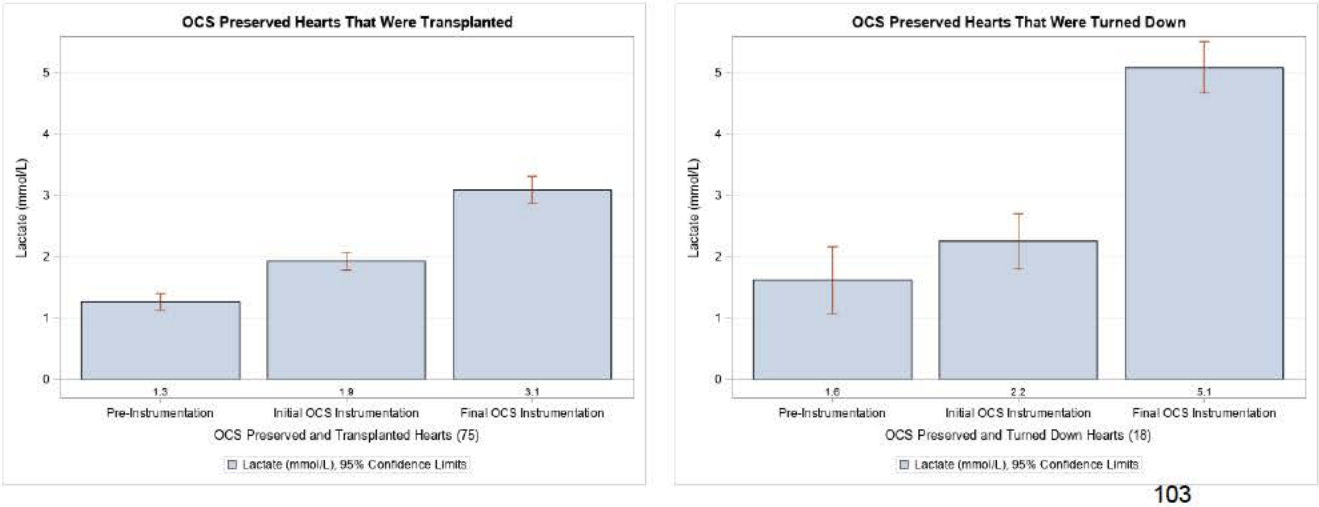
	Donor hearts turned down for transplant (n = 18)	Transplanted donor hearts (n = 75)
Mean time from CC to the start of donor heart perfusion (min)	31 ± 7	30 ± 8
Mean total OCS – Heart System perfusion time (min)	299 ± 76	279 ± 83
Mean aortic pressure (mm Hg)	83.2 ± 6.9	80.8 ± 8.0
Mean coronary flow rate (ml/min)	805 ± 45	786 ± 54
Mean final lactate level (mmol/L)	5.07 ± 0.82	3.09 ± 0.94

CC = Cross clamp. Coronary flow for transplanted hearts does not include values for 10 hearts where the PA cannula was disconnected; CF for turned-down hearts does not include values for 7 hearts where the PA cannula was disconnected.

The proportion of turned-down hearts with ECCT ≥ 4 as the only investigator-cited entry criterion was similar to the proportion of transplanted hearts having ECCT ≥ 4 as the only investigator-cited inclusion criterion. These hearts did not have any identified donor-specific anatomical or functional abnormalities identified at the time of procurement. There were 39% of turned-down donor hearts with the criterion of downtime ≥ 20 minutes, and downtime ≥ 20 minutes was a criterion in 28% of transplanted donor hearts.

Starting (in vivo) lactate levels were similar for transplanted and turned down hearts (Figure 19).

Figure 26: Lactate Levels for Transplanted and Turned-Down Hearts with final lactate 4-5 mmol/L*



Final arterial lactate was ≥ 5 mmol/L in only 8 of 18 turned down hearts (44%). Ten (10) of the hearts' final lactate levels were less than the protocol's implantation threshold value of 5 mmol/L (3.5-4.9 mmol/L). FDA identified 16/75 transplanted hearts (21%) with final lactate levels 4-5 mmol/L. OCS Heart support durations were similar for hearts with elevated but sub-threshold final lactate levels (Table 50).

Table 66: OCS Heart Perfusion Times for Turned-Down and Transplanted Hearts

Final lactate 4-5 mmol/L*	Mean Perfusion (min)	Median Perfusion (min)
Turned-down hearts (n=10)	319	286
Transplanted hearts (n=16)	312	298

*One turned-down heart had a final lactate of 3.5 mmol/L

In response to an FDA query, TransMedics explained that investigators elected transplantation of the hearts with a final lactate 4-5 mmol/L because they had had CF, AOP, and lactate trends that were generally stable or (for lactate) declining at the end of the perfusion period, unlike with turned-down hearts. FDA reviewed line data for lactate, CF and AOP of all OCS Hearts. FDA disagrees that lactate, CF, and AOP trend data were clinically different between the turned-down and transplanted hearts that had final lactate levels between 4-5 mmol/L. For example, note the similarity of CF, OCS Heart perfusion time, and lactate profile between Donor organs for Subject (b) (6) (transplanted heart) and Subject (b) (6) (turned down heart).

Figure 27: Subject (b) (6) (transplanted 2/2017)
Donor (b) (6) : 48 y/o female, A+, head trauma, ECCT ≥ 4 hours

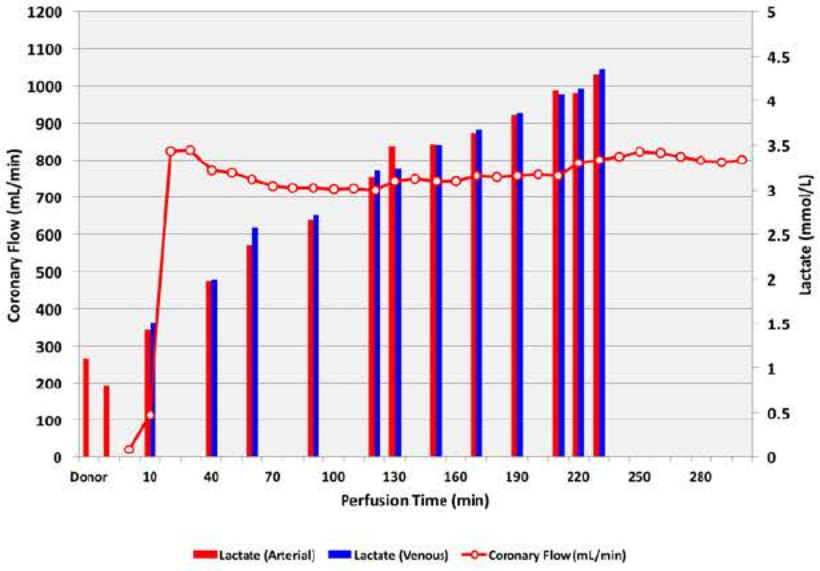
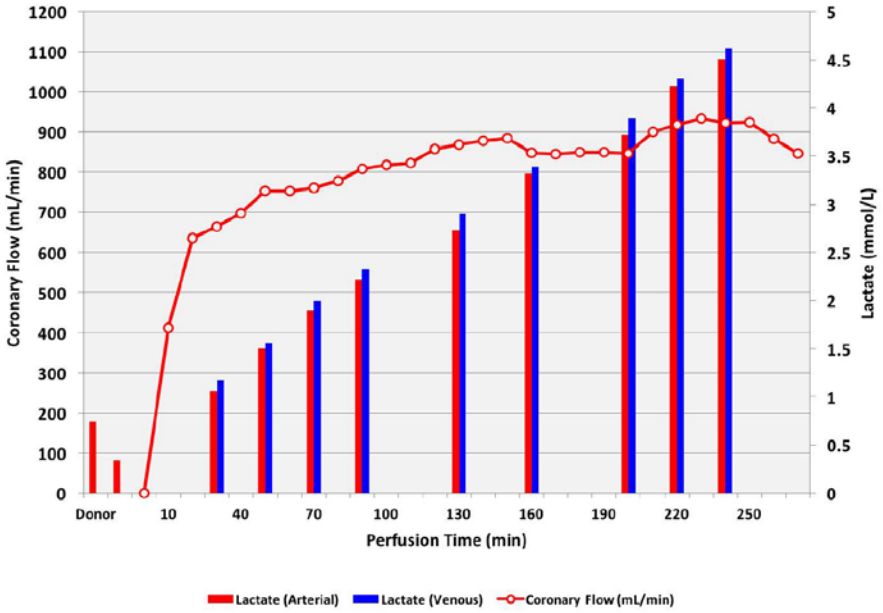


Figure 28: Subject (b) (6) (turned-down 6/2017)

Donor (b) (6): 52 y/o female, O-, cerebral hemorrhage, ECCT ≥ 4 hours, LVEF 60%



Panel: The sponsor's proposed Instructions for Use state:

> "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… The turn-down of [donor hearts] is a reflection of this new capability."

The sponsor suggests that standard-criteria donor hearts turned-down in PROCEED II because of rising lactate had "undiagnosed pre-retrieval pathologies that render these hearts to be considered "non-standard" and represent potential high risk to patients." FDA does not believe the data support this conclusion. In EXPAND, 18 donor hearts were turned-down after OCS Heart device preservation; lactate level was the principle criterion for not continuing to transplantation after preservation of the donor organ. Even if rising lactate on the OCS Heart device was a valid biomarker of an organ at risk for poor outcome after implantation, neither PROCCED II nor EXPAND was designed to assess whether OCS Heart preservation was causal to any degree for the worsening metabolic state that rising lactate may reflect. FDA views the lactate data as hypothesis-generating. FDA also believes that turn-down of a donor heart will not always be a benign event and can expose patients to important safety risks (such as in patients who undergo sternotomy but in whom heart transplant is not performed, as was observed in PROCEED II). The Panel will be asked to discuss the use of lactate as a determinant for not transplanting accepted donor hearts.

8.3 EXPAND CAP turned-down Hearts

Four (4) EXPAND CAP OCS Heart System-preserved donor hearts (9%) for 4 recipients were turned down for transplant by investigators after preservation with the device. The reason for turn-down was "transplanting surgeon or designee is clinically unsatisfied with donor heart condition/performance on OCS System at final evaluation" for 3 hearts, and lactate > 5 mmol/L for 1 heart (although two hearts had lactate levels > 5 mmol/L). Three of the 4 enrolled recipients were transplanted off-study, and the fourth remained on the waitlist as of August 26, 2020.

All 4 turned-down hearts had the sole donor heart inclusion criterion of ECCT ≥ 4 hours, and an LVEF ≥ 60% at time of acceptance (via UNOS forms). The average pre-perfusion cold ischemic time was 29.5 ± 4.8 min, and the average perfusion time was 328.5 ± 48.9 min (Table 67). One turned-down heart(b) (6)) appeared to have the PA cannula disconnected (no or low coronary flow recorded) for up to 3 hours.

Table 67: Turned Down Donor Heart Characteristics

Site	Subject ID (UNOS ID)	Final Arterial Lactate (mmol/L)	EF (UNOS)	Donor Inclusion Criteria	Pre-Perfusion (min)	Perfusion time (min)
(b) (6)	b) (6)	3.92	65%	ECCT ≥ 4 hours	29	256
		7.89	68%	ECCT ≥ 4 hours	32	392
		6.27	65%	ECCT ≥ 4 hours	22	322
		4.81	60%	ECCT ≥ 4 hours	36	344
MEAN					**29.5 ± 4.8**	**328.5 ± 48.9**

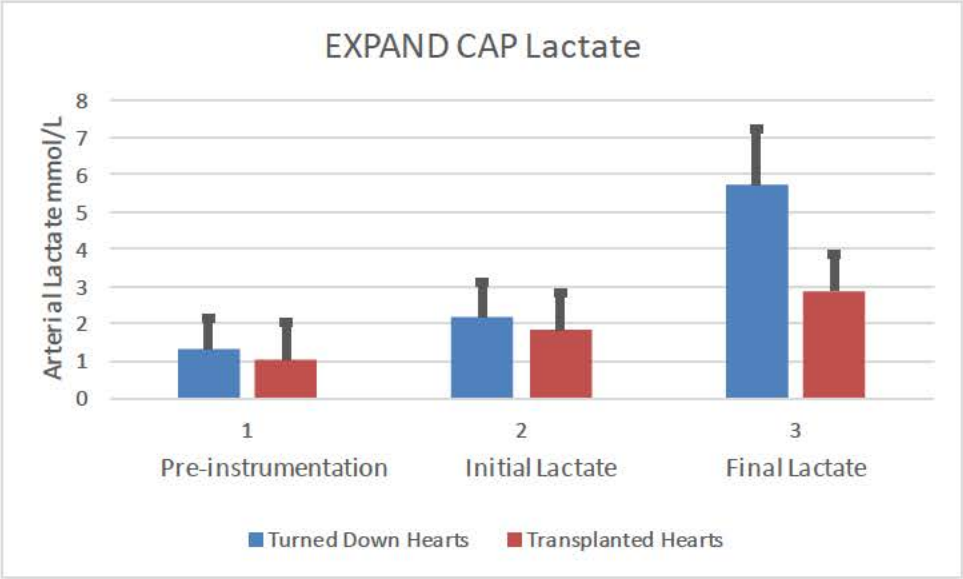
Mean and median perfusion times for the turned-down hearts and transplanted hearts are shown in the Table below:

Table 68: Perfusion Times Turned-Down and Transplanted Hearts

	Mean Perfusion (min)	Median Perfusion (min)
Turned-down hearts (n=4)	329	333
Transplanted hearts (n=41)	278	278

Pre-instrumentation and initial lactate levels were similar between the turned down and transplanted hearts, and final lactate levels were higher in turned down hearts (Figure 29).

Figure 29: EXPAND CAP Arterial Lactate



Of note, there were only 4 hearts out of the 45 supported on the OCS Heart System in EXPAND CAP that had final lactate levels > 5mmol/L. Two of these hearts were transplanted, and one of these 2 transplanted hearts had a pre-instrumentation level of 5.25 mmol/L (Table 69).

Table 69: EXPAND CAP Hearts with Lactate > 5 mmol/L

Site	Subject ID	UNOS ID	Final Lactate (mmol/L)	Outcome
(b) (6)	b) (6)		6.33	Tx
			7.59 (pre-instrumentation lactate 5.25)	Tx
			7.89	TD
			6.27	TD

TD = Turned down heart; Tx= Transplanted heart

8.4 FDA Clinicopathologic Analysis Background

Effective organ preservation is a major determinant of graft outcome after transplantation. Following explantation, a donor heart is subjected to ischemia, and the use of cooling and preservation solutions (cold static preservation) slow the progression of ischemic/hypoxic tissue injury. Unsatisfactory heart preservation may itself cause myocardial damage characterized by various forms of myocyte necrosis (coagulative, myocytolytic and contraction band). Widespread interstitial hemorrhage indicative of reperfusion injury/infarction may also be observed (4). Following transplantation, the restoration of oxygenated blood flow (reperfusion) can itself worsen organ damage.

Ischemia-reperfusion injury (IRI) is defined as cardiomyocyte damage secondary to the restoration of myocardial blood flow (5). The pathophysiologic mechanisms of IRI are complex and involve calcium overload, ATP depletion, the release of oxygen free radicals, mitochondrial swelling and rupture, and sarcolemmal rupture. These developments lead to the cascade of myocardial damage and cardiomyocyte dysfunction followed by necrotic cell death, all of which are most pronounced immediately after reperfusion (6-10).

FDA conducted an analysis of PROCEED II, EXPAND, and EXPAND CAP turned-down hearts to provide insights into concerns regarding ineffective organ preservation or potential myocardial damage associated with donor heart perfusion using the OCS Heart System.

Methods: The clinical study protocols indicated that non-transplanted donor hearts were to be examined by the transplant center qualified cardiac transplant pathologist and a central core lab. Eighteen (18) EXPAND hearts, 4 EXPAND CAP hearts, and 5 PROCEED II hearts were rejected for transplantation following OCS Heart support. Pathology reports from 2 core pathology labs were provided for FDA review. Pathology reports from the EXPAND core pathology labs (b) (6) were provided for 17 of the 18 turned down EXPAND hearts (1 heart – from site 10, (b) (6) - was returned to the Medical Examiner's Office in (b) (6) [at the request of the medical examiner] for medico-legal post-mortem examination due to the cause of death). Pathology core lab reports were provided for the 5 PROCEED II turned-down hearts (b) (6) and 4 EXPAND CAP turned-down hearts ((b) (6) . Antemortem clinical information regarding the donors was provided to the (b) (6) pathologist but not to the (b) (6) pathologist.

EXPAND and EXPAND CAP turned-down hearts: FDA performed an independent review of cardiac pathology reports from donor hearts that were perfused on the OCS Heart System but were subsequently turned down for transplantation. In addition, the following information was compiled from medical records and case report forms (when available and provided by the Sponsor) from these donor heart patients: basic demographic data; medical history leading to brain death; hospital course information including vital signs, laboratories, and cardiac assessments (including echocardiograms and cardiac catheterizations); study enrollment criteria; brain death to cross-clamp time; OCS Heart System perfusion time; mean aortic pressure; mean coronary flow; lactate level assessment, and reason(s) for turn down of the donor heart for transplantation.

Cardiac pathologic findings in EXPAND and EXPAND CAP study hearts that were turned down for transplantation (pathology reports in Appendix F and Appendix G).

The Sponsor provided cardiac pathology reports for 17 of 18 EXPAND and 5 EXPAND CAP OCS – Heart System perfused hearts that were turned down for transplantation; one EXPAND report was missing. Evidence of acute diffuse or multifocal ventricular myocardial damage was seen in 20 of 21 hearts, characterized by contraction band necrosis, coagulative necrosis, myocyte hypereosinophilia, myocyte wavy fiber change, and interstitial edema. None of these hearts had significant coronary atherosclerosis except for one specimen, which had severe triple vessel obstructive coronary disease.

The remaining heart showed healing subendocardial infarcts, consistent with myocardial damage prior to heart perfusion with the OCS Heart System.

Cardiac pathologic findings in PROCEED II trial hearts that were turned down for transplantation (pathology reports in Appendix E)

There were 5 OCS Heart System perfused hearts that were turned down in PROCEED II. Cardiac autopsy findings in these 5 PROCEED II hearts showed acute diffuse myocardial damage in 3 cases and focal myocardial damage in one case. Per review of the case report forms (5 donors) and medical records (4 donors; medical records not available for 1 donor) provided by the sponsor, heart donor patients were hemodynamically stable and deemed clinically suitable for transplant (per the trial enrollment criteria), and all 5 had a normal LV ejection fraction 1 to 5 days prior to heart explant.

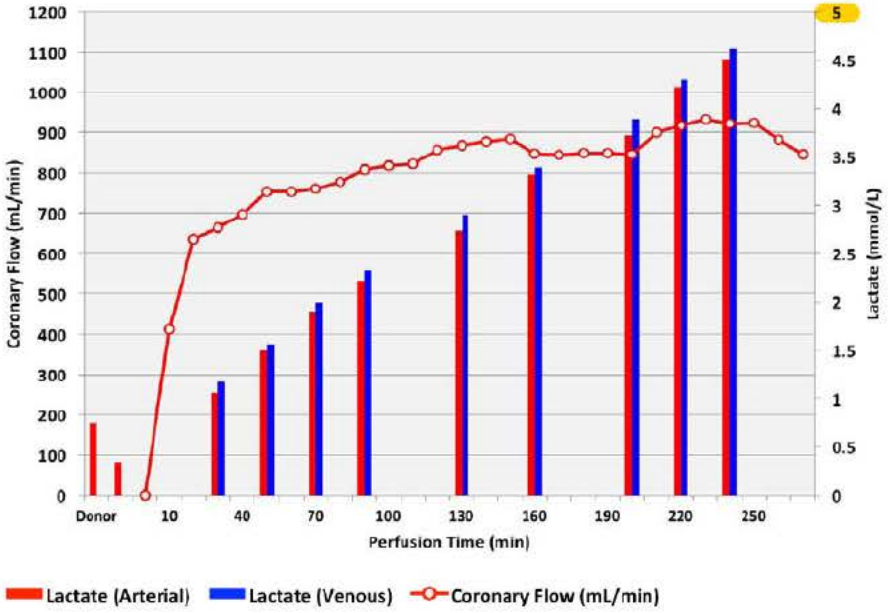
Clinicopathologic correlation and interpretation of findings

Pathologic analysis of turned-down PROCEED II, EXPAND, and EXPAND CAP donor hearts that had normal left ventricular function in the immediate antemortem period by echo (n=20) provides insights into the limitations of the OCS Heart System to provide effective organ preservation. There were 4 PROCEED II, 12 EXPAND, and 4 EXPAND CAP hearts that were turned down for transplantation, which had an echocardiography-documented LV ejection fraction ≥55% within 1 to 2 days antemortem. During this period, available medical record vital signs flowsheets showed no prolonged episodes of hemodynamic instability.

Cardiac autopsy findings in 18 of these 20 hearts showed acute diffuse ventricular myocardial damage in 12 hearts (PROCEED II, n=3; EXPAND, n=6, and EXPAND CAP, n=3) and acute multifocal ventricular myocardial damage in 6 hearts (EXPAND, n=5; EXPAND CAP n=1). Of the two remining hearts without acute multifocal ventricular or diffuse myocardial damage, one PROCEED II heart had a congenital bicuspid aortic valve, and one EXPAND heart had acute and healing myocardial infarcts. In 7 of the 11 EXPAND hearts with acute diffuse or multifocal myocardial damage, the peak lactate level was <5 mmol/L.

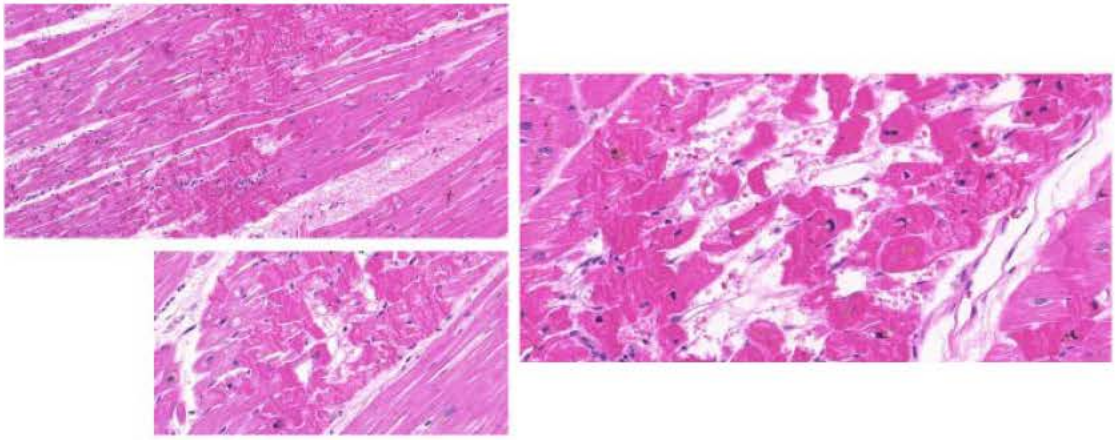
An example of an EXPAND turned-down heart that demonstrated diffuse myocardial damage following OCS – Heart perfusion was Donor (b) (6), Subject (b) (6). The donor was a 52-year old man with a hemorrhagic stroke. Cardiac catheterization showed only coronary luminal irregularities, and echocardiography within 48 hours prior to cardiectomy showed a left ventricular ejection fraction of 60%. Vital signs prior to cardiectomy were stable. The OCS-Heart perfusion time, coronary flow, and lactate levels are shown below:

Figure 30: Subject (b) (6) (Turned-Down Heart)



The core lab pathology report noted, "Sections throughout all of the myocardial defects noted grossly show severe and extensive (~25% of myocyte area) changes of ischemic injury that range from contraction band to coagulative-type necrosis with microscopic foci of tissue dissolution in the center of the damaged areas. The damage is most severe in myocardial defects 2 and 3 from the left lateral ventricle and near the septum where early tissue dissolution is seen but can be seen in nearly all defect and non-defect heart tissue samplings." Representative photomicrographs are shown in Figure 31.

Figure 31: Ventricular myocardial histologic sections from Subject (b) (6) (Turned-Down Heart) showing diffuse contraction band necrosis and occasion myocytes with coagulation necrosis



Insights in to Early EXPAND study Transplant Recipient Deaths from Pathologic Findings in Turned Down EXPAND Hearts

There were 12 EXPAND transplant heart recipients that died within 1-year of transplant. Of these 12 patients, 4 were diagnosed with acute severe primary graft dysfunction that directly contributed to death; three cases occurred within the first 24 hours, and 1 within 48 hours. Pre-transplant echocardiograms showed normal LVEF for 3 of these 4 hearts (UNOS donor forms; echo data not provided for one of these hearts). In these 4 cases, the mean time from cross-clamp to the start of donor heart perfusion on the OCS – Heart System was 26 ± 5 mins (range 19 to 33 minutes), the mean total OCS Heart System perfusion time was 224 ± 75 minutes (range 100 to 292 minutes) and the mean post-perfusion time was 84 ± 26 minutes (range 50 to 114 minutes). The mean aortic pressure and coronary flow rate was 80.2 ± 3.2 mmHg (range 78.4 to 85.8mmHg) and 813 ± 43 ml/min (range 775 to 881 ml/min), respectively. The mean maximal lactate level was 3.14 ± 0.85 mmol/L (range 2.54 to 4.59 mmol/L). Comments in the narrative summaries stated that mortality was "possibly related to preservation."

The occurrence of acute severe primary graft dysfunction in these cases raises the possibility of ineffective organ preservation by the OCS Heart System device.

Limitations

Limitations to the cardiac pathologic analysis include that not all source clinical and pathologic materials were provided and thus not reviewed by FDA. In addition, there was incomplete antemortem medical record access to core lab pathologists for clinicopathologic correlations. As acknowledged by the pathologists (phone call with FDA on May 13, 2019) and FDA, there is uncertainty in estimating of the timing of ischemic myocardial injury (e.g., occurring antemortem or during OCS Heart System perfusion); there are no animal studies that describe the features and time course of myocardial pathologic changes that occur when hearts are perfused with the device. Lastly, brain death is associated with myocardial dysfunction in some patients, which is believed to be due to excessive catecholamines/sympathetic storm. Limited cardiac pathologic studies, predominately in animals, show focal myocytolysis, coagulative necrosis, and contraction bands. Therefore, in the turned down OCS Hearts, it is possible that some pathologic changes may have been associated with brain death. However, in turned down donor hearts with *normal antemortem LV function and without significant antemortem structural abnormalities*, the frequent observation of multifocal or diffuse myocardial damage following device use supports the conclusion that perfusion with the OCS Heart device can in some cases be associated with significant myocardial injury.

Summary of Pathology Data

The pathologic analysis of turned down donor hearts with: (1) stable antemortem hemodynamics; (2) normal (or essentially normal) cardiac anatomy and normal ventricular function by echocardiography; and (3) cardiac autopsy findings of acute diffuse or multifocal myocardial damage raise the possibility that in an important proportion of cases, the OCS Heart System device did not provide effective organ

preservation or may have severely damaged what would have been a viable graft for transplant. These findings raise the possibility that use of the OCS Heart System could lead to the unintended result of reducing the pool of donor hearts.

Panel: The Panel will be asked to comment on the pathologic analysis of PROCEED II, EXPAND, and EXPAND CAP turned-down hearts and implications regarding the effectiveness of organ preservation and/or potential myocardial damage associated with donor heart perfusion using the OCS Heart System, and the potential device impact on the pool of available donor hearts.

9. Clinical Summary

The OCS Heart System concept, and in particular its use in an extended criteria donor heart category, is intended to advance the field of cardiac transplantation. However, due to multiple significant limitations in the design, execution, and analyses of the PROCEED II, EXPAND and EXPAND CAP studies, an assessment of device benefit-risk is challenging. The panel will be asked to comment and vote on the overall safety, effectiveness and benefit-risk profile of the OCS Heart System.

10. Post-approval Study

Note: The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA. The presence of a post-approval study plan or commitment does not alter the requirements for premarket approval and a recommendation from the Panel on whether the benefits of the device outweigh the risks. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding potential post-approval studies, for the Panel to include in the deliberations, should FDA find the device approvable based upon the premarket data.

In the event that the OCS Heart System is approved (thus a reasonable assurance of safety and effectiveness is demonstrated), FDA recommends that additional data collection be required as a condition of approval for this first-of-a-kind device to continue evaluation of the short, mid and long term (through 5 years) safety and effectiveness of the OCS Heart System. Please see Appendix H for a more detailed description of the post-approval plan proposed by TransMedics, as well as FDA's comments/concerns with this plan.

Summary

TransMedics has proposed to conduct two post-approval studies to continue evaluating the performance of the OCS Heart System:

1. OCS Heart Post Approval Registry: A 175 patient, single-arm, prospective, multicenter, observational post-approval registry. Donors and recipients will be consistent with the approved indication for use and will reflect the eligibility criteria of the Heart EXPAND study. Patients will be followed for12 months post-transplantation. Patient outcomes will be evaluated at months 24 - 60 post-transplantation by accessing data from the UNOS database.

Discussion

Study Endpoint and Hypothesis

The primary endpoint for the proposed registry is patient survival from cardiac graft-related death at 12 months. In addition, the sponsor proposes to assess primary graft failure and patient death (all-cause) within the initial 30 days post-transplant as a safety endpoint. Other endpoints to be evaluated are freedom from cardiac graft-related death, freedom from all-cause death, freedom from re-transplantation through 5 years and donor utilization rate.

FDA Comment: Cardiac graft-related death at 12 months was a non-adjudicated, post-hoc analysis performed by the sponsor for (b)(4). FDA has suggested that a major OCS Heart System concern is longer-term survival, possibly related to injury to donor hearts that might have been well-preserved using standard of care cold static preservation. As such, FDA recommends evaluating both patient survival and graft survival at 1 year as a composite primary endpoint.

The sponsor proposes to conduct a hypothesis test to demonstrate that 12-month patient survival from cardiac graft-related death in this registry study is greater than a performance goal (PG) of 86%. The proposed PG was based on OPTN data of 1-year freedom from cardiac graft-related death for standard-criteria donor hearts preserved on cold storage (98%). TransMedics has proposed a margin of 12% for the OCS Heart preserved standard-criteria donor heart assessment which results in PG of 86% (i.e., 98% - 12%).

FDA Comment: FDA believes that a PG of 86% is low considering a post-hoc, unadjudicated analysis of cardiac graft-related survival at 12 months in the EXPAND Trial was associated with a 95% survival rate.

Panel: The Panel will be asked to discuss the appropriateness of the proposed primary endpoint (e.g.,12-month survival from cardiac graft related death) and other follow-up assessments in order to evaluate the long-term safety and effectiveness of the device. Additionally, the panel will be asked to discuss the performance goal for the primary endpoint.

2. OCS Heart EXPAND trial Post Approval Follow-Up Data Analysis: A single-arm, prospective, observational post-approval study in which outcomes obtained from the existing national Scientific Registry of Transplant Recipients (SRTR)/OPTN database for subjects transplanted in the Heart EXPAND IDE Trial will be obtained and analyzed through 5 years. The study population will be compromised of all seventy-five (75) transplanted recipients in the Heart EXPAND IDE trial.

FDA continues to work with TransMedics to address concerns with the proposed post-approval data collection plans to ensure that if the device is approved, remaining questions about device performance will be sufficiently addressed.

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