Discussion/Questions to Panel

EXPAND Study Design and Conduct

The following important trial design and study conduct issues may affect the interpretability and validity of the study dataset and analyses:

Study Design

a. Design: EXPAND was carried out as a single-arm investigation and there were limited data for subjects not included in a Per Protocol (PP) population (equivalent to Transplant Recipient [TR] population).

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

EXPAND Study Design and Conduct – cont'd

c. Effectiveness: The primary effectiveness endpoint was defined as allograft survival at POD 30 following transplantation in the absence of severe Primary Graft Dysfunction (PGD) involving the left or right ventricle in the first 24 hours post-transplantation. This endpoint was tested against a performance goal of 65%, and moderate PGD was not included.

d. Donor heart inclusion criteria: EXPAND's donor heart eligibility criteria do not identify organs that are uniformly deemed unacceptable for transplantation if preserved using cold static preservation techniques, raising the possibility that there was overlap between hearts accepted for OCS Heart perfusion in the EXPAND (including EXPAND CAP) and PROCEED II studies.

EXPAND Study Design and Conduct – cont'd

Study Conduct

e. Revisions to Donor Heart Inclusion Criteria: The sponsor's dataset reflects EXPAND donor heart inclusion criteria that were revised after data lock and after the PMA had undergone FDA review. The donor heart inclusion criteria modifications affected 20 donor hearts. Additional criteria were assigned in all instances where donor heart inclusion criteria were revised, of which 17 modifications changed the assignment of single-criterion hearts to multiple-criteria hearts. There were no donor hearts for which criteria were removed.

f. PGD Classification Changes: Despite objective definitions of PGD intended to standardize classifications using data collected within 24 hours after completion of transplant surgery, multiple site-identified PGD classifications in EXPAND were changed during the adjudication process, which took place months or years after the transplant. These changes raise the possibility that individual endpoint determinations in EXPAND were subjective to some degree.

EXPAND Study Design and Conduct – cont'd

1. Please discuss the impact of these study design and study conduct issues on assessing the safety and effectiveness and benefit-risk profile of the OCS Heart System.

EXPAND Inclusion Criteria

The EXPAND Study intended to utilize hearts that otherwise would not have been accepted for transplant. However, EXPAND's donor heart eligibility criteria do not identify organs that are uniformly deemed unacceptable for transplantation if preserved using cold static preservation techniques.

EXPAND and CAP Donor Heart Single Inclusion Criterion

Donor inclusion criteria	TR EXPAND Hearts (n=75)	TR CAP Hearts (n=41)	TR Pooled Hearts (n=116)
ECCT ≥ 4 *% of Single Criterion Hearts*	18 *45%*	15	33 *52%*
EF ≥ 40% ≤ 50%	10	1	11
Downtime ≥ 20 min	4	4	8
LVH (> 12 ≤ 16 mm)	3	1	4
Luminal irregularities, no CAD	2	-	2
≥ 55 y/o	2	-	2
EtOH	1	3	4
TOTAL	**40** *(53%)*	**24**	**64** *(55%)*

TR = Transplanted

EXPAND Inclusion Criteria – cont'd

2. Please discuss whether there was overlap between the standard hearts studied in the PROCEED II randomized trial and hearts studied in EXPAND and EXPAND CAP. If you believe there was overlap between "extended" and standard donor hearts, please discuss the effect that commercial availability of the OCS Heart device may have on the availability of acceptable donor hearts for transplantation, and overall long-term survival.

Transplantability

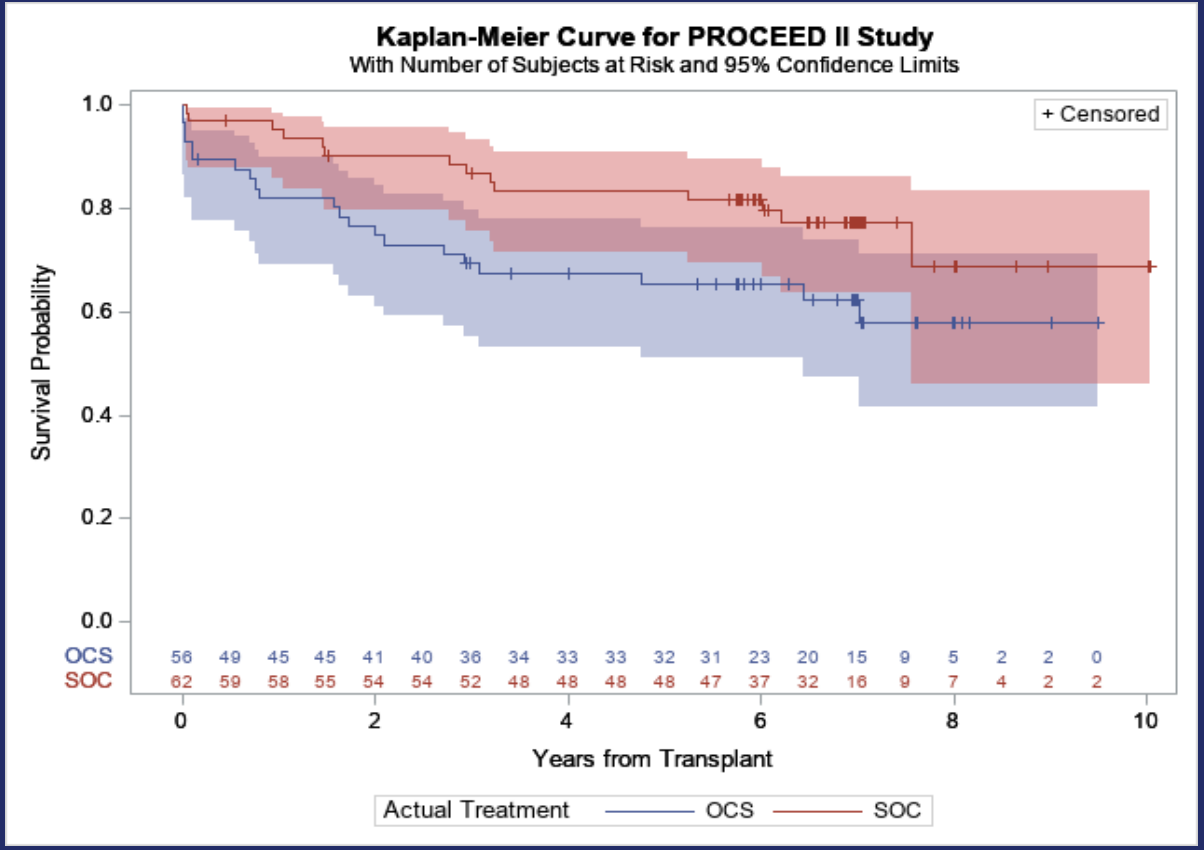
OCS Heart arterial lactate level was the principle criterion given for not continuing to transplantation after preservation of the donor organ on the OCS Heart System for 5 PROCEED II donor hearts, 18 EXPAND donor hearts, and 4 EXPAND CAP donor hearts. FDA is unclear as to the utility of this metric as the principle criterion for determining transplantability, noting that 2 EXPAND CAP hearts were transplanted with arterial lactate levels of 6.3 and 7.8mmol/L at the end of OCS perfusion (one of which had an initial arterial lactate > 5mmol/L), as well as the many (>50%) turned down hearts that had final arterial lactate levels < 5mmol/L.

Transplantability cont'd

3. Please discuss the accuracy and reliability of lactate levels as the principle determinant for not transplanting accepted donor hearts. In your discussion, please consider the impact on patients who undergo sternotomy in preparation for transplant in whom the transplant was not performed due to lactate levels greater than the target range.

PROCEED II and EXPAND Study Analysis

Long term survival: In PROCEED II, the observed all-cause mortality rate following transplantation was higher after donor heart preservation using the OCS Heart device than after cold static preservation (SOC); the magnitude of the survival benefit for patients transplanted with standard of care hearts was clinically meaningful and persisted over the long term.



PROCEED II and EXPAND Study Analysis

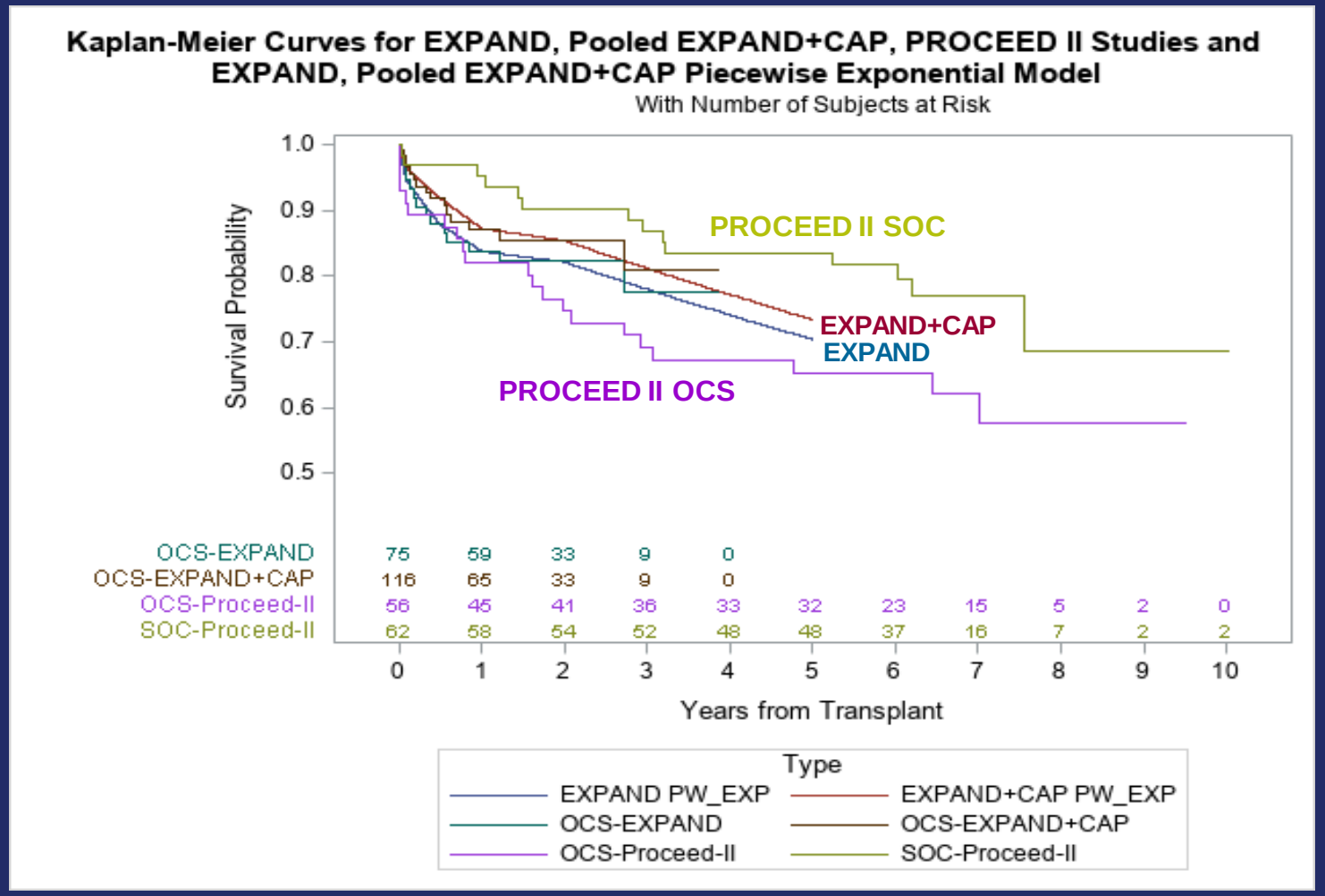
The Kaplan-Meier survival analysis for EXPAND demonstrates survival rates of 83.8% at 1-year, 82.2% at 2 years, and 77.7% at 3-years, and the Kaplan-Meier survival analyses for EXPAND+CAP demonstrates survival rates of 87.2% at 1-year, 85.5% at 2 years and 80.8% at 3-years. The Table below includes contemporary survival rates for 1 and 3 years from the 2019 Scientific Registry of Transplant Recipients Annual Report, just published a few weeks ago.

Time Post-Transplant	PROCEED I Survival		EXPAND Survival	EXPAND+CAP Survival	SRTR* Survival
	OCS	SOC	OCS	OCS	
1-year	82.0%	95.1%	83.8%	87.2%	92-93%
2-year	74.7%	90.2%	82.2%	85.5%	
3-year	69.2%	86.9%	77.7%	80.8%	85-86%

**Survival 2019 SRTR Heart Annual Report – published 2021*

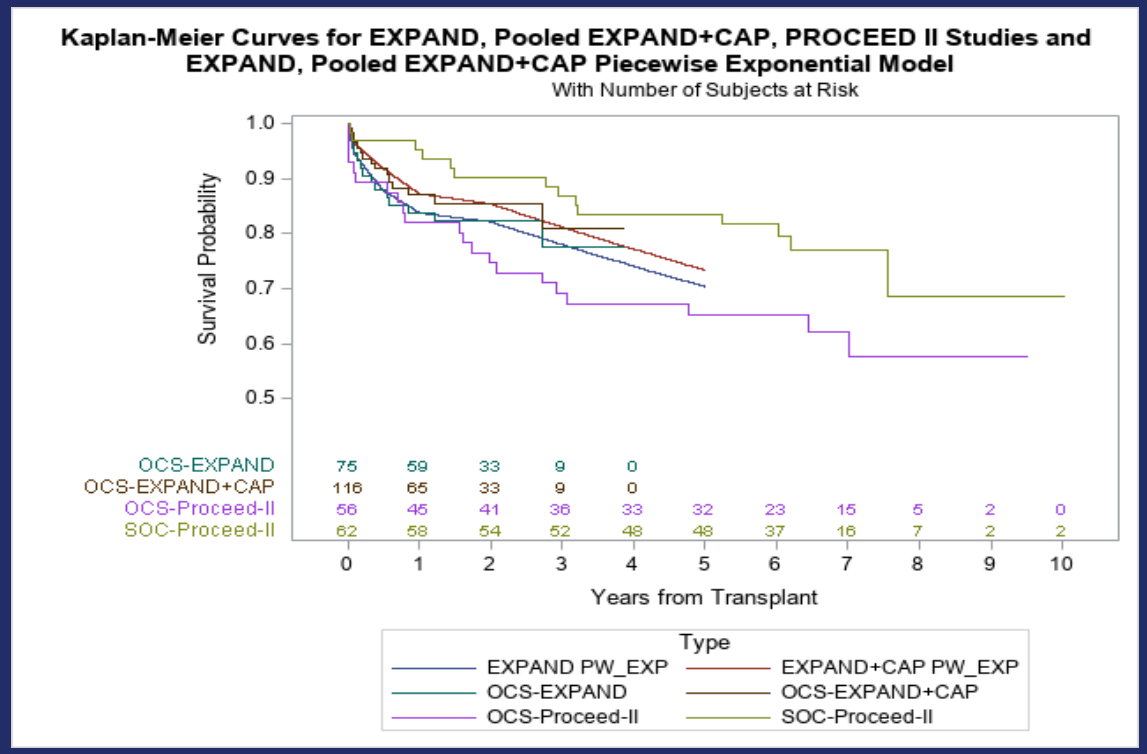
PROCEED II and EXPAND Study Analysis

Figure 22 (from the Executive Summary) combines the K-M curves for PROCEED II, EXPAND, EXPAND+CAP, and the Piece-Wise modeling and is shown here:



PROCEED II and EXPAND Study Analysis – cont'd

4a. Please discuss the clinical implications of these results with respect to whether there is a longer-term benefit of preserving donor hearts using the OCS Heart System.



Time Post-Transplant	PROCEED II		EXPAND	EXPAND+ CAP	SRTR*
	OCS	SOC	OCS	OCS	
1-year	82.0%	95.1%	83.8%	87.2%	92-93%
2-year	74.7%	90.2%	82.2%	85.5%	
3-year	69.2%	86.9%	77.7%	80.8%	85-86%

**Survival 2019 SRTR Heart Annual Report – published 2021*

PROCEED II and EXPAND Study Analysis – cont'd

Wait Times

According to the Scientific Registry of Transplant Recipients (SRTR), nearly 40% of patients newly listed in 2018 underwent heart transplantation within 3 months, and approximately 57% had undergone transplantation within one year of listing. In 2019, 3% of subjects died while waiting for a donor organ, while 12% were removed from the list for reasons other than death or transplantation; 6-month mortality for patients removed from the list was approximately 20%. Although EXPAND was not prospectively designed to use the SRTR as a comparator, the EXPAND OCS Heart group had shorter wait times than patients in the SRTR.

4b. Please discuss the strengths and limitations of this comparison, and whether the results of EXPAND indicate a probable benefit of shorter wait times. In addition, please discuss the wait time analysis in the context of post-transplantation long-term survival.

PROCEED II and EXPAND Study Analysis – cont'd

FDA believes that collectively the analyses from PROCEED II, EXPAND, and EXPAND CAP may suggest sub-optimal survival when the device is used to preserve structurally and/or functionally "standard" donor organs whose only criterion for device use is preservation time anticipated to be prolonged (≥ 4 hours).

4c. Please discuss whether you believe the device, if approved, has demonstrated sufficient safety and effectiveness for donor hearts considered non-standard on the basis of anticipated prolonged preservation time only

Pathophysiology and Pathology

In PROCEED II, compared to patients transplanted with SOC donor hearts, the group of patients transplanted with OCS Heart System-perfused donor hearts had a numerically greater need for mechanical circulatory support post-transplant, more frequent acute rejection episodes, lower average cardiac index, longer average ICU stay, and longer average initial hospital duration. In EXPAND and EXPAND CAP, pathology results from hearts perfused on the OCS Heart System but turned down for transplant suggested that the OCS Heart System may have contributed to myocardial damage in some donor hearts.

5. Please discuss the implications of these pathophysiologic and pathologic observations on the effectiveness of heart preservation and/or potential myocardial damage associated with donor heart perfusion using the OCS Heart System. In addition, please discuss the potential impact of hearts turned down for transplantation following OCS Heart perfusion on the pool of available donor hearts.

Indications for Use

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

- Expected cross-clamp or ischemic time ≥ 4 hours due to donor or recipient characteristics (e.g., donor-recipient geographical distance, expected recipient surgical time); **or**
- Expected 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 ≤ 16 mm); or
  - Donor angiogram with luminal irregularities but no significant coronary artery disease (CAD).

Indications for Use – cont'd

6. Please discuss whether the EXPAND Study donor heart inclusion criteria (or an inclusion criteria subset) identifies a reasonable set of objective "extended" or "expanded" heart criteria that define hearts not routinely used for transplantation after cold static storage. If so, please provide additional discussion as follows:

Indications for Use – cont'd

a. Based on the available data, please discuss whether the objective set of inclusion criteria that can be defined as "extended" donor hearts intended for preservation on the OCS Heart System will result in an increase in donor heart utilization and acceptable survival for recipients.

b. Please discuss whether the available study data provide a reasonable assurance of safety and effectiveness for donor hearts defined by each of the individual donor heart criteria. If not, please explain your concerns.

Benefit/Risk

The EXPAND single-arm study was designed to leverage the results of the PROCEED II randomized, controlled trial for standard criteria donor hearts, to allow for expanded indications for use in non-standard criteria donor hearts. However, reasonable assurance of safety and effectiveness was not determined for the OCS Heart System for the preservation and transplantation of standard criteria donor hearts. In FDA's opinion, the OCS Heart System studied under the EXPAND clinical study for "extended criteria" donor hearts was not designed as a stand-alone clinical study, and it is for this reason that the FDA is considering the results from both the PROCEED II and EXPAND studies in its assessment of the OCS Heart System benefit-risk assessment.

Benefit/Risk

The OCS Heart EXPAND study met its 30-day primary endpoint of transplant recipient and allograft survival in the absence of severe primary heart graft dysfunction (PGD) in the first 24 hours post-transplantation (tested against a performance goal of 65%). However, lower survival with OCS preserved standard hearts (sustained over the long-term), high turn-down rate for hearts preserved on the OCS Heart System (13% overall), potential injury to some donor hearts being preserved on the OCS System, and the subjectivity of the "extended" donor heart inclusion criteria creating potential overlap with standard hearts, raise concerns related to how the OCS System may affect the pool of viable donor hearts available to recipients, as well as overall longer-term survival for heart transplant patients.

Benefit/Risk

7. Given the totality of the evidence regarding the effectiveness and safety profile of the OCS Heart System, i.e., the results of the pivotal randomized PROCEED II study, the single-arm EXPAND study and the supplementary EXPAND CAP data, please discuss whether the benefits of the OCS Heart System outweigh the risks.

Proposed Post-Approval Study

Note: This requested discussion item related to the proposed Post-Approval Study 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.

Post-approval studies are often required at the time of approval of a PMA to address remaining questions or provide information on the continued safety and effectiveness of the approved device. These studies are not intended to provide initial support for reasonable assurance of safety and effectiveness, as that determination must be established prior to device approval. If a PAS is requested, the sponsor has proposed two post-approval studies to continue to evaluate the performance of the OCS Heart System:

- A 175 patient, single-arm, prospective, multicenter, observational post-approval registry with follow-up out to 12 months, and outcomes out to 5 years; and

- A single-arm, observational post-approval follow-up data analysis in which outcomes obtained from the existing national Scientific Registry of Transplant Recipients (SRTR)/OPTN database for the 75 subjects transplanted in EXPAND will be obtained and analyzed out to 5 years.

Proposed Post-Approval Study

8. Please comment on whether additional study objectives, design features, or surveillance are recommended for the Post-Approval Studies. Specifically, please discuss the appropriateness of the proposed primary endpoint (e.g.,12-month survival from cardiac graft related death), the 86% performance goal (considering a post-hoc, unadjudicated analysis of cardiac graft-related survival at 12-months in EXPAND was 95%), as well as other follow-up assessments necessary to evaluate the long-term safety and effectiveness of the device.