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TransMedics® Organ Care System™ (OCS™) HEART System

(b) (4)

Sponsor Executive Summary

Meeting of the Circulatory System Devices Panel

April 6, 2021

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1. OVERVIEW OF CLINICAL EVIDENCE SUPPORTING THE OCS HEART SYSTEM

1.1. Introduction

This document is intended to present to the panel:

- All clinical and scientific evidence supporting the approval of OCS Heart System PMA for the proposed indications below;
- TransMedics' response to FDA's key points highlighted in the FDA Panel Executive Summary; and
- The scientific and clinical rationales behind TransMedics' positions if different from the FDA's.

This section provides the high-level evidence and associated conclusions in support of this PMA for the OCS Heart System. In addition, this Overview outlines the 3 key fundamental differences between TransMedics and FDA that will be addressed in detail throughout the entire document. These differences can be summarized as follows:

- The OCS Heart EXPAND trial and supporting data from the ongoing EXPAND Continued Access Protocol (CAP) should be considered as the main data set supporting the OCS Heart PMA for the proposed indications. The PROCEED II trial was a historical, smaller sample sized trial designed for a different clinical indication. Importantly, there are substantial differences in donor/recipient characteristics and risk factors, as well as device and clinical use model differences that makes it appropriate to consider these two trials completely independently of each other.
- When evaluating the effectiveness of a preservation technology like the OCS Heart System, consideration of long-term survival must be accompanied by a robust cause of death analysis and specifically the assessment of cardiac/graft-related long-term survival. This is to avoid the potentially significant confounding clinical variables in the long-term clinical course of heart transplant recipients (e.g., immunosuppressives, previous history of VAD use and its associated medical complications on end-organ function).
- Due to the significant shortage of suitable donor hearts for transplantation, very limited number of end-stage heart failure patients are placed on the national waiting list for transplantation. Importantly, those who make it to the waiting list are not guaranteed a heart transplant and approximately 16% of patients die while waiting on the U.S. heart transplant waiting list every year. Thus, increasing donor heart utilization from existing and new donor pools that are seldom utilized for transplantation due to historical limitations of cold ischemic storage is a significant clinical and public health benefit. Data from the OCS Heart EXPAND trial and OCS Heart EXPAND CAP clearly demonstrated significant increase in utilization of these type of donor hearts that are seldom transplanted today with good post-transplant clinical outcomes. This clinical public health benefit of increasing the number of usable donor hearts for transplantation should be a seminal part of the overall assessment of the safety and effectiveness of the OCS Heart System for the proposed indication for use.

1.2. Proposed Indication for Use for the OCS Heart System

In this PMA, TransMedics is seeking approval for the following indication for use 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 cross-clamp or total ischemic time of ≥ 2 hours AND one or more of the following criteria:*
>   - *Donor age ≥ 55 years; or*
>   - *Donors with history of cardiac arrest and downtime of ≥ 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) – LV septal or posterior wall thickness of > 12 ≤ 16 mm; or*
>   - *Donor angiogram with luminal irregularities but with no significant coronary artery disease (CAD).*

1.3. Clinical Background

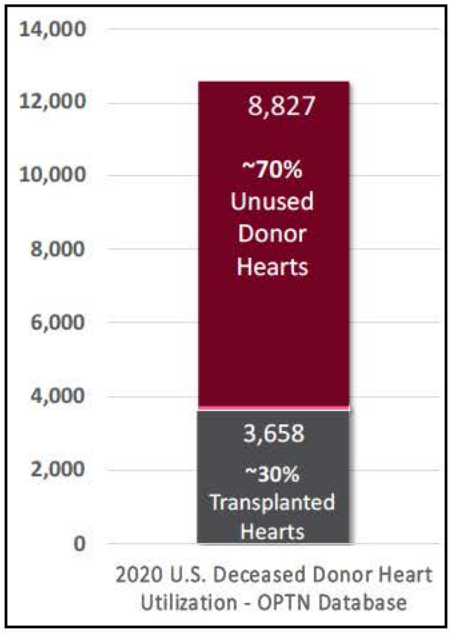
Heart transplantation is the only curative therapy for end-stage heart failure. Unfortunately, only approximately one-third of donor hearts are currently utilized annually for transplant in the U.S. (OPTN 2019). The utilization of donor hearts is severely restricted by the limitations of cold ischemic storage of donor organs, which include:

- Severe time-dependent ischemic injury to the donor heart, which limits the geographical time/distance for procuring donor hearts for transplantation;
- No capability to optimize the donor heart from the non-physiologic negative environment of brain death; and
- No ability to assess donor heart viability for transplantation after it has been retrieved from the donor body.

These limitations of cold storage restrict utilization to standard criteria donor hearts (i.e., younger donors that are within a short time/distance from the recipient and have the fewest donor risk factors). These and other factors leave ~70% of available deceased donor hearts

unutilized annually. This low utilization restricts the number of patients who can receive a life-saving heart transplant (Figure 1).

Figure 1: U.S. Donor Heart Utilization for Transplants from Deceased Donors



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. The OCS Heart System perfuses donor hearts with warm, oxygenated, nutrient-enriched blood, while maintaining the organs in a beating, functioning state. The OCS Heart System's innovative technology was designed to comprehensively overcome the historical limitations of cold storage. One of the primary clinical advantages of the OCS Heart System is the ability to expand the utilization of donor hearts by enabling the use of donor hearts currently unutilized due to limitations of cold storage for patients who are in need for heart transplantation to treat their end-stage heart failure condition.

The OCS Heart System consists of:

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

Figure 2: Components of OCS Heart System

1.4. Overall Clinical Development & Regulatory History of the OCS Heart System

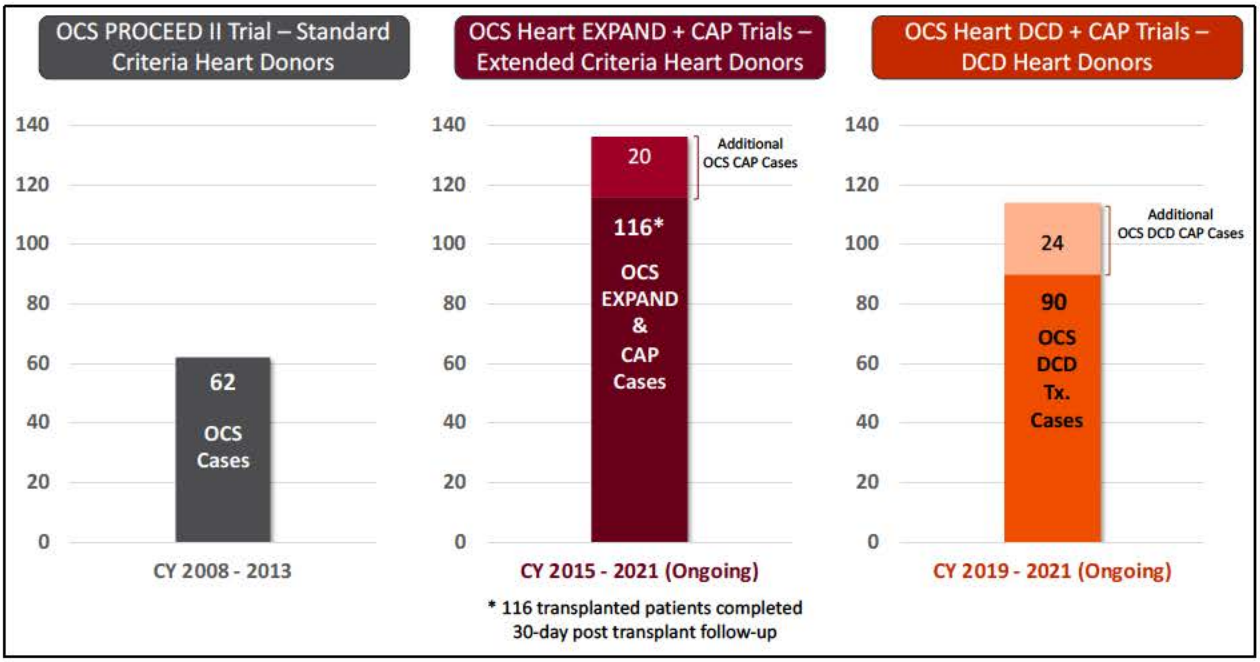
In the U.S., the OCS Heart System has been or is being studied in three U.S. IDE pivotal clinical trials to develop the clinical evidence to support the use of the OCS Heart System for heart transplantation for different indications: extended, standard, and DCD donor heart criteria.

- **The OCS Heart EXPAND Trial & Continued Access Protocol (CAP) IDEs:** The OCS Heart EXPAND trial, as well as the associated OCS Heart EXPAND CAP data, represent the primary data set supporting this PMA and the proposed clinical indications. The OCS Heart EXPAND trial transplanted 75 subjects between 2015-2018 with a focus on preserving and transplanting extended criteria Donor after Brain Death (DBD) hearts that are seldom utilized for transplantation today due to the limitations of cold storage. The objective 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 expand donor heart utilization for transplantation. The trial met its primary endpoint and provides substantial evidence of the safety and effectiveness of the OCS Heart System for the proposed intended clinical indication.

  The OCS Heart EXPAND CAP is on-going and provides additional strong supportive evidence for the safety and effectiveness of the OCS Heart System for identical extended criteria DBD donors as the OCS Heart EXPAND trial. As of the date of database closure, 41 patients transplanted in the OCS Heart EXPAND CAP have been followed for a minimum of 30 days post-transplant. This results in a combined total of 116 patients who have received extended criteria DBD hearts preserved on OCS in the U.S. and have been followed up for a minimum of 30 days post-transplant. In this Panel Executive summary, we have presented an analysis of the OCS Heart EXPAND trial data, followed by a presentation of the combined data for the OCS Heart EXPAND trial and the OCS Heart EXPAND CAP. Pooling these data are appropriate because the two trials followed the same protocol.

- **The OCS Heart DCD Trial IDE:** The OCS Heart DCD trial is a first of its kind pivotal study that was granted "Breakthrough Device" status from FDA given its potential for substantial public health impact. This trial initiated enrollment in Dec 2019 and is focused on hearts from Donors after Circulatory Death (DCD) to demonstrate a potential expansion of the donor pool in the U.S. to include DCD hearts. To date, the trial has completed enrollment of a total of 180 patients: 90 DCD heart transplants using the OCS Heart System and 90 DBD heart transplants serving as the control arm. If successful, the results from the OCS Heart DCD trial will be the subject of a future FDA regulatory review for approval of the DCD clinical indication for the OCS Heart System.
- **The PROCEED II Trial IDE:** This trial was the first ever pivotal trial conducted of the OCS Heart System or any other extracorporeal perfusion device for donor organs. PROCEED II included 62 OCS and 66 control patients transplanted between 2008-2013 and focused on standard criteria donor hearts. The goal of this trial was to demonstrate non-inferiority of 30-day clinical outcomes to standard of care (SOC) cold storage. The trial met its primary effectiveness and safety endpoints; however, the old PMA was withdrawn because of fundamental disagreements with FDA on the interpretation of an unplanned, post-hoc analysis of unadjudicated long-term survival data obtained from the observational UNOS registry. However, there were many fundamental learnings from the PROCEED II trial that resulted in significant changes to the device design and the clinical management of the donor hearts on OCS to minimize the user learning curve and maximize/standardize post-OCS myocardial protection of the donor heart (from removal of the donor heart from the OCS Heart System to the release of the aortic cross-clamp in the recipient). These modifications were applied in the subsequent clinical trials of the OCS Heart System discussed above (OCS Heart EXPAND trial, OCS Heart EXPAND CAP, and OCS Heart DCD trials) and in commercial use of the OCS Heart System outside the U.S.

Figure 3: OCS Heart U.S. Clinical and Regulatory Programs



NOTE: FDA's Panel Executive summary has implied that there is substantial overlap in demographic characteristics between the donor hearts in the PROCEED II and OCS Heart EXPAND trials and that the donor hearts in the OCS Heart EXPAND trial and OCS Heart EXPAND CAP are "generally clinically similar to the donors in PROCEED II." However, this assertion is not supported by the data from the two trials, as well as by an analysis of donor characteristics in the UNOS/SRTR national database of standard criteria donor hearts preserved using cold storage. (See summary results table below and details in Section 6.1.13, Section 6.2.5, and Section 6.4 of this Executive Summary.) TransMedics respectfully asserts that OCS Heart EXPAND trial and OCS Heart EXPAND CAP are the most relevant data to support the proposed clinical indications in this PMA and that the donor hearts included in the OCS Heart EXPAND and OCS Heart EXPAND CAP trials are extended criteria donors, those seldom transplanted in the U.S. today as supported by data from the UNOS/SRTR national database.

To specifically address whether there is a substantial overlap in donor demographics/ characteristics between OCS EXPAND & CAP population compared to standard criteria donor hearts in PROCEED II trial, TransMedics performed an analysis of donor data from the national UNOS/SRTR database of standard criteria donors transplanted today using cold storage compared to the combined OCS Heart EXPAND + CAP population.

For this analysis, the N=138 donor hearts in the OCS Heart EXPAND + CAP population were compared to UNOS/SRTR data on 10,873 donor hearts transplanted over the time period of January 2015-March 2019, which excludes any recipients of OCS donor hearts. This is an analysis of donor characteristics/risk factors only, to specifically address the above issue and does not include post-transplant outcomes.

Summary results are listed in Table 1 below. The data demonstrate that the OCS Heart EXPAND + CAP donor hearts are not routinely transplanted on cold storage in the U.S. today. This is further demonstrated when considering donors transplanted in the U.S. on cold storage with two or more criteria (which comprised 45% of donor hearts in the OCS Heart EXPAND + CAP population). As shown in Table 1, of the 10,873 donor hearts preserved on cold storage:

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

Table 1: Donor Characteristics for OCS Heart EXPAND + CAP Heart Population vs. UNOS/SRTR Hearts Transplanted 2015- March 2019

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

These data, in conjunction with the UNOS donor match run described in Table 2 below, show that the donor hearts transplanted in the combined OCS Heart EXPAND + CAP population are not routinely transplanted in the U.S. today on cold storage and that the OCS Heart System allowed these hearts to be transplanted, leading to potential expansion of the utilization of donor hearts for transplantation. This is an important clinical consideration in the assessment of the benefits and risks of the OCS Heart System to increase the number of successful heart transplants in the U.S.

Outside of the U.S., the OCS Heart System has been CE-marked and approved for commercial use in the EU since 2006. It is also approved for use in Australia, Canada, Saudi Arabia, United Arab Emirates, Israel, Taiwan, and Kazakhstan. Worldwide, it has been used to preserve over 1,071 transplanted donor hearts, of which over 302 were DCD hearts.

1.5. Summary Overview & Results of OCS Heart EXPAND Trial

In this PMA for the OCS Heart System, TransMedics is seeking an indication for the resuscitation, preservation, and assessment of donor hearts that would likely not be utilized for transplantation in the U.S. due to limitation of cold storage ("extended criteria donor hearts"), and that would benefit from OCS Heart perfusion and assessment to potentially enable them to

be utilized for transplantation. To be clinically robust and maximize clinical value and safety for potential transplant recipients in our trial, TransMedics sought the advice and guidance of leading U.S. academic heart failure cardiologists and transplant surgeons to define the specific types of donor hearts to be used in the OCS Heart EXPAND protocol which were reflected in the donor eligibility criteria for this trial.

To support this indication, TransMedics designed and executed the OCS Heart EXPAND trial (IDE G140111), the first clinical trial of a technology to facilitate the transplantation of extended criteria donor hearts. The OCS Heart EXPAND trial results are the primary data set supporting this proposed indication. The OCS Heart EXPAND trial is a prospective, multi-center single arm study of 75 transplanted recipients at 9 investigational sites in the U.S. The OCS Heart EXPAND trial enrolled recipients from the national heart transplant waiting list that reflect the latest clinical practices in the treatment of heart failure (e.g., use of ventricular assist devices (VADs)), as well as contemporary practices in heart transplantation. The OCS Heart EXPAND trial evaluated the use of the OCS Heart System on donor hearts for which the device will be indicated following approval. Specifically, the OCS Heart EXPAND trial targeted donor hearts with one or more of the following characteristics:

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

The primary endpoint for the OCS Heart EXPAND trial was a composite of patient survival at 30 days post-transplant and incidence of severe ISHLT Primary Graft Dysfunction (PGD) within 24 hours post-transplantation. The pre-specified performance goal (PG) for success was 65%, which was derived based on the published literature for standard criteria heart transplantation incidence of severe PGD of ~30% and on UNOS national database statistics for 30-day patient mortality of ~5%. Standard criteria outcomes were used to develop the PG, given the lack of published literature on post-transplant clinical outcomes for recipients with the proposed

donor heart characteristics in the OCS Heart EXPAND trial at the time the clinical protocol was being developed.

Designing this trial as a randomized controlled trial (RCT) was not feasible or ethical for the proposed indication, given the fact that donor hearts that were enrolled in the OCS Heart EXPAND trial are seldom used for transplantation today due to inherent limitations of ischemic cold storage. It would not be feasible or ethical to require that surgeons preserve these donor hearts on cold storage and it would have subjected potential recipients in the control arm to an unacceptably high risk of poor post-transplant outcomes, including death.

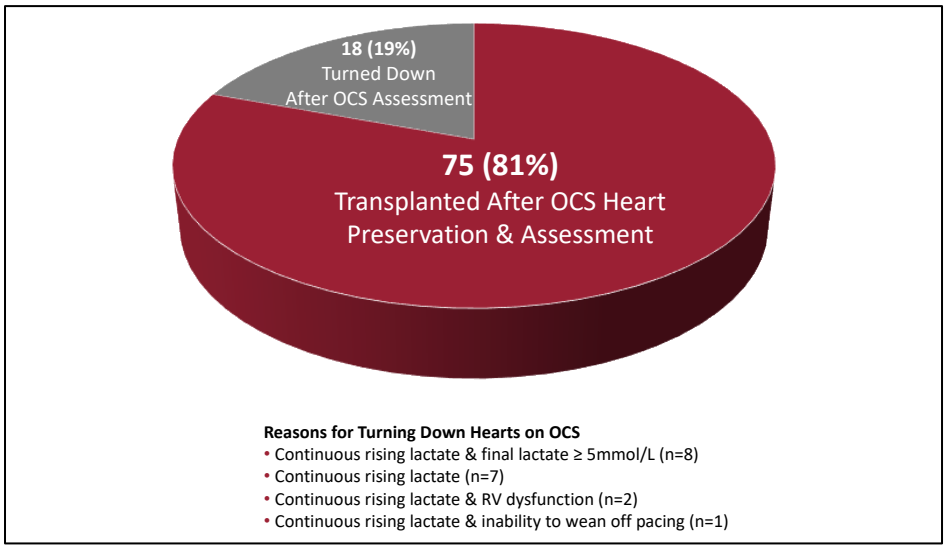
The primary safety endpoint for the OCS Heart EXPAND trial was the average number of heart graft-related SAEs (HGRSAEs) within the initial 30 days post-transplant, consisting of moderate or severe ISHLT LV or RV PGD or primary graft failure requiring re-transplantation within the first 30 days post-transplant. All instances of PGD and HGRSAE were independently adjudicated by the Medical Monitor. A statistically-driven safety endpoint in the OCS Heart EXPAND trial was not necessary since the primary endpoint already incorporated the most clinically relevant safety outcomes, i.e., severe PGD and patient survival.

Survival was assessed at 30 days, initial hospital discharge if longer than 30 days, and up to 1-year post-transplant.

1.5.1. Summary of the Clinical Results of the OCS Heart EXPAND Trial

- Seventy-five (75) of the 93 (81%) donor hearts instrumented on OCS were successfully transplanted into a recipient. The results demonstrate that the use of OCS Heart System resulted in high utilization (as defined in the protocol) of donor hearts that would seldom be utilized today using cold static storage.

Figure 4: Donor Heart Utilization in the OCS Heart EXPAND Trial



- It is important to note that of the 75 donor hearts transplanted in the OCS Heart EXPAND trial, 47% of the transplanted donor hearts met more than one of the above eligibility criteria, indicating more challenging donor conditions than what were anticipated at the time the trial was designed. This was further validated by the results of the UNOS donor match run data for donor hearts that were enrolled in the OCS Heart EXPAND trial, which showed an average of 66 refusals for transplantation before they were accepted by an OCS Heart EXPAND trial center (Table 2). For reference, from 2007-2014, the median number of refusals for heart transplants in the U.S. was 2 (Baran, et al., 2019), which underscores that these hearts would have probably gone unutilized for transplantation if they were not enrolled in the OCS Heart EXPAND trial.

Table 2: Donor Heart Offers Refusals Prior to Acceptance in the OCS Heart EXPAND Trial

	UNOS Donor Heart Match Run Data for OCS Heart EXPAND Perfused Hearts (N = 93)
Mean number of Refusals per donor heart (Mean ± SD)	66 ± 90
Median number of Refusals per donor heart (range)	29 (0 – 379)

- There were 18 donor hearts that did not meet transplantability criteria on the OCS Heart System. All of these turned down donor hearts exhibited unstable and rising lactate trends despite multiple attempts by the users to optimize perfusion parameters. Figure 5 below illustrates the mean lactate values for all 18 hearts that were turned down after OCS Heart assessment as compared to the OCS Heart lactate profile for the donor hearts that were transplanted in the OCS Heart EXPAND trial. A relationship between rising lactate levels in OCS Heart perfusate and post-transplant graft failure or dysfunction was shown by Hamed, et al., 2009. Ever since, the measurement of lactate during OCS Heart perfusion has been a guiding principle in managing a donor heart on the OCS Heart System in addition to overall clinical judgment based on contractility and perfusion parameters. This principle was incorporated into the OCS Heart EXPAND trial and all OCS Heart commercial use outside of the U.S.

  The clinical case summary for each of these turned down organs and the status of the intended recipients, along with the expert independent core pathologist assessment, are provided in Table 23.

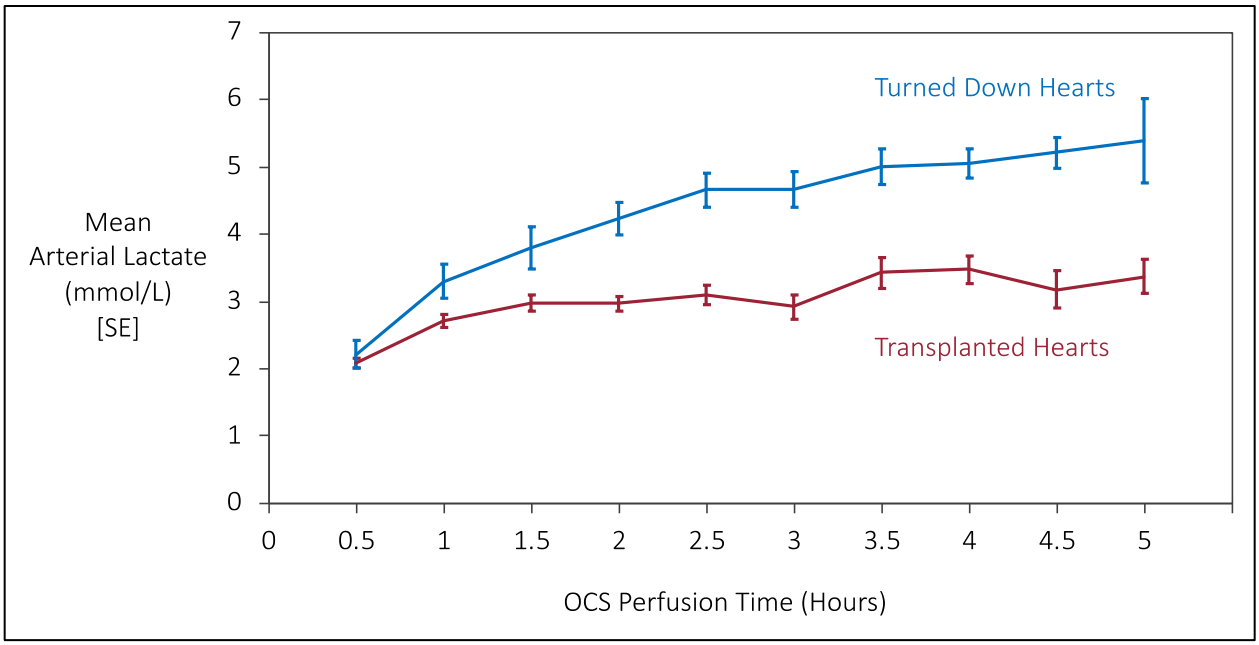
- FDA's Panel Executive Summary asserts that, based on FDA's interpretation of pathology reports, that OCS Heart System may have caused damage to the donor hearts during perfusion that may have caused these hearts to be turned down for transplantation. TransMedics respectfully refutes this assertion based on the following objective clinical facts:

  - Brain death is associated with significant physiologic changes that could show as pathological findings of a donor heart on histological examination of the myocardium;

- The donor hearts studied in the OCS Heart EXPAND trial were hearts with significant risk factors that made them highly unlikely to be used for transplantation. Many of these risk factors could contribute to pathological findings in histological examination of the myocardium;
- The FDA analysis disregards the potential of these hearts being inherently damaged by the insult of brain death and associated risk factors described above;
- Many of the subjective findings cited by FDA such as "myocardial petechiae" are commonly seen in routine cardiac bypass open heart surgeries and with no major clinical negative impact on heart function; and
- To our knowledge, there have never been any published or presented reports of any clinical or pre-clinical data directly or indirectly linking OCS Heart System to myocardial injury during perfusion.

See Section 6.1.22 for a more detailed discussion of the pathology findings in OCS Heart EXPAND.

Figure 5: Mean Arterial Lactate Trend on the OCS Heart System for All Turned Down Donor Hearts Compared to Hearts that were Transplanted in EXPAND Trial



- The OCS Heart EXPAND trial met its primary endpoint with an 88% success rate on the primary effectiveness composite endpoint ($p<0.0001$) (Figure 6). With regard to the components of the composite endpoint, 95% of recipients survived through 30 days post-transplant and the incidence of severe ISHLT PGD was 10.7%, which is comparable to or lower than contemporary rates of severe Heart PGD published in the literature (see Figure 7 below).

Figure 6: Primary Composite Endpoint Results for the OCS Heart EXPAND Trial: Survival at 30 Days Post-transplant and Absence of ISHLT Severe PGD (LV or RV) Post-transplant

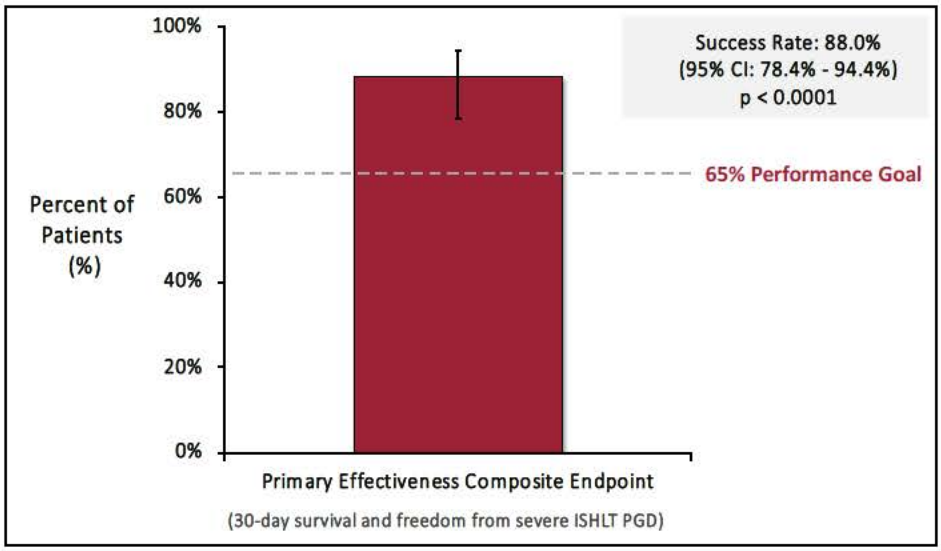
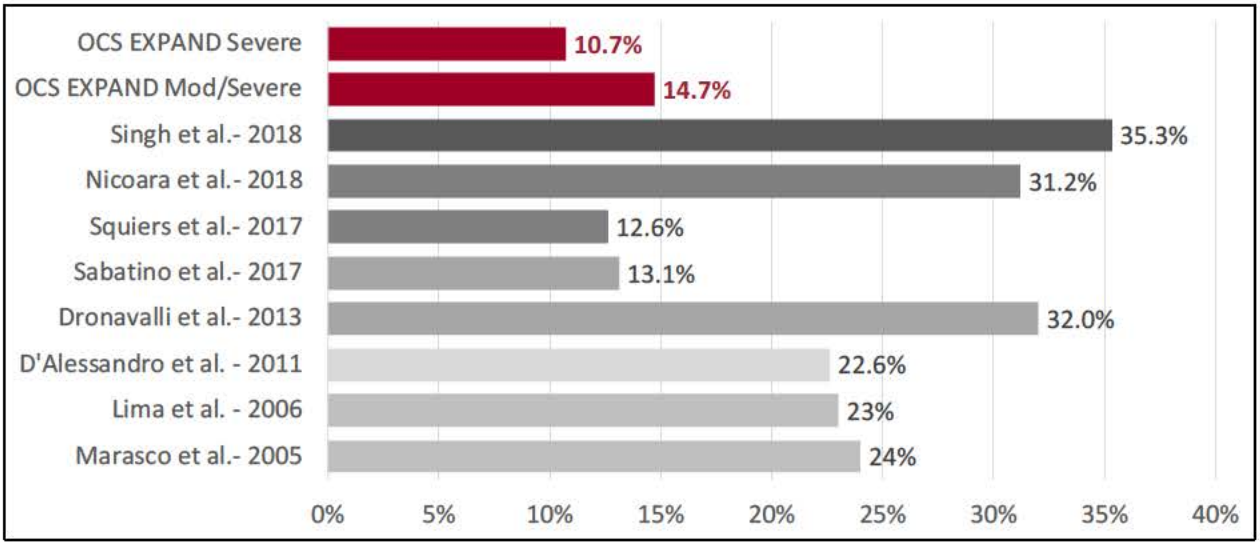


Figure 7: Incidence of Severe and Moderate & Severe Heart ISHLT PGD Observed in OCS Heart EXPAND Trial Compared to Published Literature



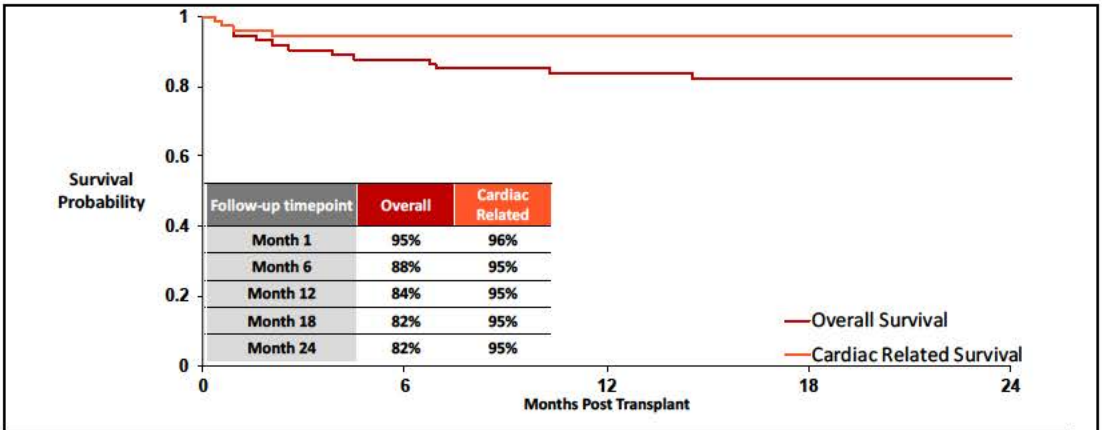
- The primary safety endpoint of the OCS Heart EXPAND trial was the number of heart-graft-related SAEs (HGRSAEs) through 30 days. The mean number of HGRSAEs per patient was 0.2 ± 0.37 (Table 3). Overall, the SAEs that occurred in the trial were consistent with those expected following standard heart transplantation and do not raise any signals for concern.

Table 3: Primary Safety Endpoint for the OCS Heart EXPAND Trial and Listing of HGRSAEs by Type

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

- All transplanted recipients in the OCS Heart EXPAND trial have been followed through a minimum of 12 months post-transplant, and all deaths through 12 months post-transplant were adjudicated by an independent Medical Monitor. In addition, survival data for the Heart EXPAND subjects were obtained from the unadjudicated UNOS national database, giving follow-up beyond 12 months for subjects who had data entered in the database. The results for overall survival and cardiac-related survival were acceptable and comparable to overall survival for standard heart transplant recipients who received donor hearts preserved using cold storage. The Kaplan-Meier analysis of overall patient survival and post-hoc analysis of cardiac graft-related survival for OCS Heart EXPAND trial patients are shown in Figure 8.

Figure 8: Kaplan-Meier Analysis of Overall Survival & Cardiac-Related Survival for OCS Heart EXPAND Trial Subjects (N=75)



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

NOTE: TransMedics believes that assessment of cardiac-related long-term survival is clinically relevant when evaluating effectiveness of heart preservation technology given the complex medical condition of heart transplant recipients and the multiple confounding variables (e.g., immunosuppression, history of VADs and associated complications) that could impact long-term survival.

It is important to note that 4 of 13 deaths (30.8% of deaths and 5% of overall trial mortality) through 14 months post-transplant in the OCS Heart EXPAND trial were due to recipient pre-existing factors and/or causes that were unrelated to the transplanted heart or the use of the OCS Heart System:

- Subject (b)(6) died on Day 29 at home due to pre-existing advanced chronic liver cirrhosis.
- Subject (b)(6) died on Day 80, and the subject likely had undiagnosed parenchymal lung disease leading to post-op acute respiratory distress disease.
- Subject (b)(6) died on Day 212 at home due to re-occurrence of pre-existing extra-cardiac amyloidosis with refractory GI bleed.
- Subject (b)(6) died 14 months post-transplant due to motor vehicle accident that is unlikely to be related to the transplant procedure or the transplanted heart.

- FDA's Panel Executive Summary includes the results of statistical modelling to extrapolate EXPAND subject survival through 5 years post-transplant.

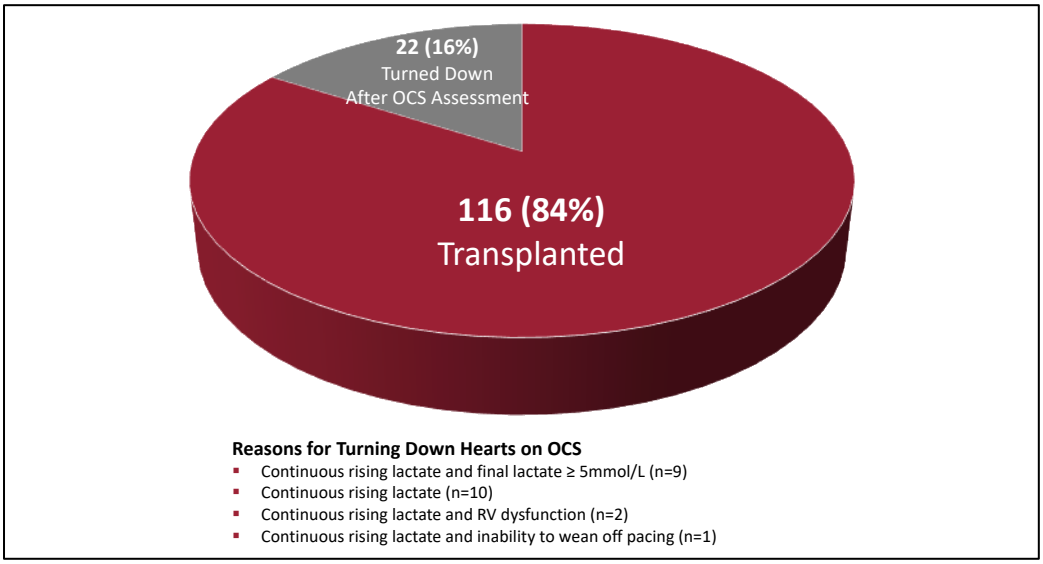
  TransMedics believes, based on statistical evidence developed by independent biostatisticians, that the models have poor predictive validity and poor reliability (wide confidence intervals) and alternative models could be developed using other methods with widely varying results from the FDA models. Therefore, TransMedics believes that these models are statistically and scientifically flawed and the discussion of the benefit-risk of the OCS Heart System should focus on the actual clinical data observed in the trial.

1.5.2. Summary of the Combined Results of the OCS Heart EXPAND Continued Access Protocol (CAP) and the OCS Heart EXPAND Trial

- In addition to the 75 transplanted patients in the OCS Heart EXPAND trial, FDA approved a continued access protocol (CAP) to allow for additional patients to be transplanted with extended criteria hearts on the OCS Heart System. As of the date of database closure, 49 donor hearts were enrolled in OCS Heart EXPAND CAP and assessed on the OCS Heart System. Four of the 49 recipients of donor hearts did not have 30-day follow-up data as of the date of database cut-off and are not included in these analyses. Therefore, 45 donor hearts were perfused and assessed and 41 were successfully transplanted. In the pooled OCS Heart EXPAND + CAP analysis population, 138 donor hearts were perfused and assessed on the OCS Heart System, and 116 of the 138

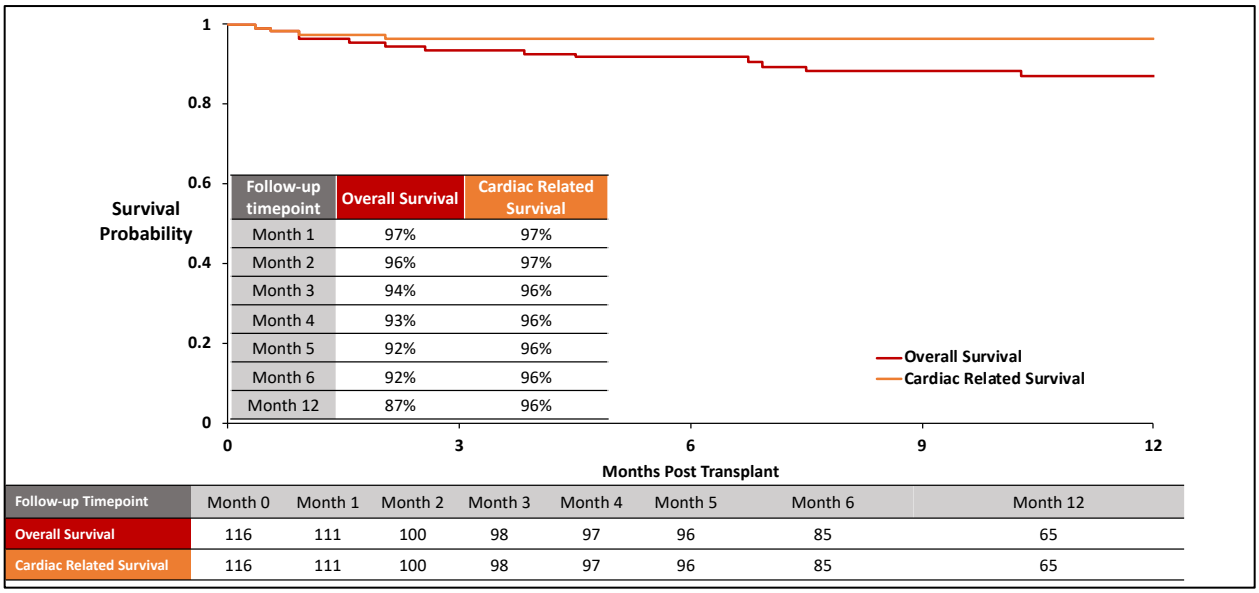
extended criteria donor hearts were successfully transplanted, giving a utilization rate (as defined in the protocol) of 84.0% (Figure 9).

Figure 9: Donor Heart Utilization in OCS Heart EXPAND Trial and OCS Heart EXPAND CAP Pooled Analysis



- In the combined analysis of the OCS Heart EXPAND + CAP population of 116 transplanted recipients, 91% of the subjects achieved success on the composite endpoint of patient survival at Day 30 post-transplantation and absence of ISHLT severe PGD (left or right ventricle).
- Regarding the secondary endpoints, the 30-day patient survival of 97% in the pooled OCS Heart EXPAND + CAP population is comparable to contemporary standard criteria heart transplant patient survival in the U.S (96%, Colvin, et al., 2020). The observed incidence of severe ISHLT PGD of 7.8% in this population is lower than contemporary rates of severe heart PGD published in the literature (Figure 7).
- Kaplan-Meier analysis of overall patient survival and post-hoc cardiac related survival for the combined OCS Heart EXPAND + CAP analysis population (116 total transplanted patients) is shown in Figure 10 below. Patient survival for OCS Heart EXPAND + CAP patients was 92% at 6 months and 87% at 12 months. The overall patient survival results are comparable to contemporary overall patient survival rates reported in the UNOS registry for recipients of standard criteria donor hearts preserved on cold storage, i.e., 92% at 6 months and 90% at one year (Colvin, et al., 2020). Post-hoc analysis of cardiac graft-related survival was 96% at 6 and 12 months, respectively.

Figure 10: Overall and Cardiac-related Patient Survival for OCS Heart EXPAND + CAP Patients Combined through 12 Months Follow-up (N=116)



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

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

- The results of the pooled analysis of the OCS Heart EXPAND + CAP population demonstrate the safety and effectiveness of the OCS Heart System for the proposed indications and demonstrate that the use of OCS Heart System may significantly increase donor heart supply for patients with end-stage heart failure in the U.S on the waiting list for a heart transplant.

1.6. Additional Historical Clinical Experience with the OCS Heart System in the U.S. & Worldwide

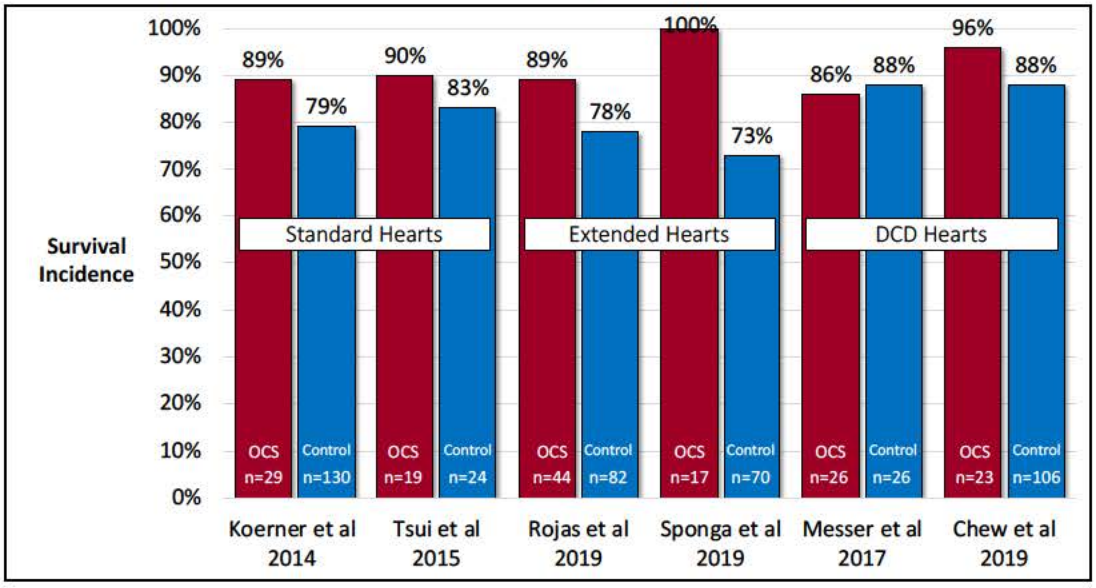
- **OCS Heart PROCEED II Trial:** Between 2008-2013, the OCS Heart System was studied for preservation of standard criteria donor hearts in PROCEED II (IDE G060127), a randomized, controlled non-inferiority study of the OCS Heart System compared to standard of care (SOC) cold storage for preservation of standard criteria donor hearts. PROCEED II was the first IDE clinical study of the OCS Heart System and the first ever pivotal trial for extracorporeal normothermic perfusion devices for donor organs. The results of the PROCEED II trial were published in The Lancet in April 2015.
  - The PROCEED II trial met its primary and secondary effectiveness endpoints and showed statistical non-inferiority to standard of care donor hearts preserved using cold storage in all analysis populations. The incidence of cardiac graft-related serious adverse events in the OCS group was shown to be non-inferior to the SOC group.
  - The protocol of the PROCEED II trial specified 30-day post-transplant follow-up. An unplanned, post-hoc, analysis of unadjudicated long-term outcome data obtained from the UNOS national heart transplant registry indicated that 19 deaths had occurred in the OCS arm and 11 deaths had occurred in the Control arm. The majority of this apparent difference in survival was not related to the

cardiac graft nor to the use of OCS Heart System. The number of patients whose cause of death was related to the cardiac graft (non-immunologic or immunologic) was the same for the two groups (4 patients in the OCS Group and 4 in the Control Group) through 5 years post-transplant.

- TransMedics elected to withdraw the previous PMA because of fundamental disagreements with FDA on the interpretation of the unplanned, post-hoc, analysis of unadjudicated long-term survival data obtained from the observational UNOS registry.
- There were many critical learnings from conducting the PROCEED II trial that resulted in significant changes to the device design and clinical management of the donor hearts on OCS to minimize the user learning curve and maximize and standardize post-OCS myocardial protection of the donor heart (from removal of the donor heart from the OCS Heart System to the release of the aortic cross-clamp in the recipient). These modifications were applied in the subsequent two clinical trials (the OCS Heart EXPAND trial and OCS DCD Heart trial) discussed above and in commercial use of the OCS Heart System outside the U.S. Detailed discussion of the PROCEED II trial results are presented in Section 6.3.

- **Published International Clinical Data on Clinical Use of the OCS Heart System in DBD and DCD Donor Hearts:** Additional supporting clinical evidence is provided by numerous peer-reviewed published clinical data on the use of the OCS Heart System outside the U.S. These studies evaluated the short and long-term survival of recipients of standard criteria, extended criteria, and DCD hearts. Long-term survival for patients who receive OCS-preserved donor hearts, with follow-up from one to five years, ranged from 86% to 100%. Figure 11 below summarizes the published long-term outcomes data for OCS Heart System use.

Figure 11: Summary of Peer-reviewed Published Clinical Data on OCS Heart System Use Outside the U.S. (OUS) Totaling 165 OCS Heart Transplants



1.7. Summary of Clinical Evidence Supporting the Approval of the OCS Heart System

Data from the OCS Heart EXPAND trial and OCS Heart EXPAND CAP provide substantial evidence of effectiveness, safety, and a favorable benefit/risk profile to support the OCS Heart System approval for the proposed clinical indication for use.

OCS Heart System Demonstrated Effectiveness:

- An analysis of risk factors for donor hearts from the national UNOS/SRTR registry data demonstrated that the OCS Heart EXPAND and OCS Heart EXPAND CAP trials enrolled donor hearts that are seldom or rarely transplanted in the U.S. today using ischemic cold storage. The use of the OCS Heart System resulted in successful transplantation of 81% and 84% of these types of donor hearts. This finding supports the benefit of the OCS Heart System to expand the donor pool to increase the number of heart transplants performed in the U.S.
- The OCS Heart EXPAND trial met its primary effectiveness composite endpoint of 30-day post-transplant patient survival and freedom from severe ISHLT PGD with an 88% success rate on the primary effectiveness composite endpoint ($p<0.0001$). The combined OCS Heart EXPAND + CAP population (N=116) met the primary effectiveness composite endpoint of 30-day post-transplant patient survival and freedom from severe ISHLT PGD with a 91% success rate on the primary effectiveness composite endpoint.
- The 30-day patient survival of 95% in the OCS Heart EXPAND trial is comparable to contemporary standard criteria heart transplant survival in the U.S. The 30-day patient survival of 97% in the combined OCS Heart EXPAND + CAP population is also comparable to contemporary standard criteria heart transplant survival in the U.S. (96%; Colvin, et al., 2020).
- The incidence of severe ISHLT PGD was 10.7% in the OCS Heart EXPAND trial and 7.8% in the combined OCS Heart EXPAND + CAP population. These rates are comparable to or lower than contemporary rates of severe heart PGD reported in the literature.
- The OCS Heart EXPAND trial long-term patient survival at 6 and 12 months post-transplant was 88% and 84%, respectively. Post-hoc analysis of cardiac graft-related survival was 95% at 6 months and 12 months post-transplant, respectively. The long-term patient survival at 6 and 12 months post-transplant in the combined OCS Heart EXPAND + CAP population was 92% and 87%, respectively. Post-hoc analysis of cardiac graft-related survival for the combined OCS Heart EXPAND + CAP population was 96% at 6 month and 12 months post-transplant, respectively. The overall patient survival results are comparable to contemporary overall patient survival rates reported in the UNOS registry for recipients of standard criteria donor hearts preserved on cold storage, i.e., 92% at 6 months and 90% at one year (Colvin, et al., 2020).
- TransMedics acknowledges the overall survival difference observed in the PROCEED II RCT based on an unplanned, post-hoc analysis of unadjudicated data from the UNOS national heart transplant registry. However, this finding is of lesser importance in assessing the effectiveness and safety of the OCS Heart System for the proposed indication because of the following:

- The proposed indication for use in this PMA is based on the specific categories of donor hearts studied in the OCS Heart EXPAND and OCS Heart EXPAND CAP trials and does not include the hearts that were the subject of PROCEED II trial.
- The PROCEED II trial differs substantially from the OCS Heart EXPAND trial which makes it clinically less relevant to the assessment of the OCS Heart proposed indication:
  - There are donor and recipient characteristics that were significantly different between PROCEED II and OCS Heart EXPAND (see Section 6.4.1 and Section 6.4.2).
  - There were major differences in the devices and use models evaluated in the PROCEED II and the OCS Heart EXPAND trials (see Section 6.4.3).
- While an overall long-term survival difference is observed in PROCEED II, the cardiac graft-related mortality through 5 years post-transplant was similar between the OCS and control arms, based on 30-day follow-up data from PROCEED II and the causes of death recorded on long-term follow-up in the UNOS registry.
- The observed difference in the PROCEED II RCT has not been reported or observed in any published study for OCS clinical use for any donor heart criteria (standard, extended, and DCD donors). Several peer-reviewed studies from different single and multi-center clinical experiences were published reporting better survival results for recipients of donor hearts preserved on the OCS Heart System from standard, extended criteria and even DCD donors (see Section 6.5).

- TransMedics has proposed a robust post-market registry to continue to expand the short and long-term clinical evidence on the OCS Heart System in the U.S. in the real-world setting. We propose to enroll an additional 175 new cases into the post-approval registry and follow patient and graft survival up-to 5 years post-transplant. The proposed post-market registry is described in Section 9 of this document.

OCS Heart System Demonstrated Safety:

- The OCS Heart EXPAND trial demonstrated the safety of the OCS Heart System. The mean number of HGRSAEs per patient was 0.2 ± 0.37. The same result was observed for combined OCS Heart EXPAND + CAP population, with a mean number of HGRSAEs per patient of 0.2 ± 0.37.
- Serious Adverse Events were typical for patients undergoing heart transplantation, and do not raise any signals for concern.
- TransMedics developed and implemented a comprehensive clinical training program that includes extensive hands-on training and a point of use proprietary iOS application with detailed step by step instructions checklists and training videos. TransMedics also maintains 24 X 7 phone support to minimize users' learning curve and ensure proper use of the OCS to maximize safety for the patients. See Section 8 of this document for a detail description of the training program.

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

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

2. BACKGROUND – CLINICAL NEED FOR OCS TECHNOLOGY

End-stage heart failure is a major public health issue in the U.S., and the incidence is estimated at 650,000 patients annually (Mancini and Colombo, 2015). Of those with heart failure, approximately 5-10% of patients are considered end-stage or advanced heart failure patients who are candidates for heart transplantation or LVADs (AHA Statistics, 2019). Heart transplantation is the treatment of choice for addressing end-stage organ failure due to its positive clinical outcomes and excellent quality of life (Stehlik, et al., 2012). The American Heart Association, the International Society of Heart and Lung Transplantation (ISHLT), the American Transplant Society and heart failure clinicians in the U.S. and worldwide recognize heart transplantation as the “gold standard” treatment and the only curative therapy for end-stage heart failure (Peura, et al., 2012; Katz, et al., 2015; Wilhelm, 2015; Mancini and Lietz, 2010; Kobashigawa, et al., 2017). The most recent literature suggests that the 1-year mortality rate for patients with end-stage heart failure is approximately 40-60% without advanced therapies (Singh, et al., 2012).

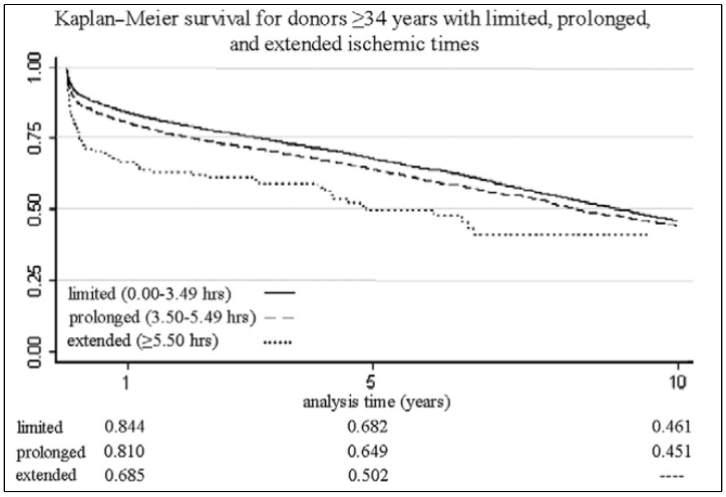
Despite this growing clinical demand, the number of heart transplants has been significantly restricted by the limitations of the standard of care for donor heart preservation - cold static storage. Despite significant progress in most aspects of heart transplantation (i.e., donor management, operative technique, post-operative care, and immunosuppressive regimens), donor heart preservation has remained cold static storage for more than 30 years.

The limitations of cold storage result in an ongoing race against the clock for heart transplant procedures and adversely affect donor heart utilization (Russo, et al., 2007; Krakauer, et al., 2005; Yeen, et al., 2013; Kobashigawa, et al., 2014). Cold storage subjects the donor heart to

time-dependent ischemic and subsequent reperfusion injuries that have the potential to impair heart function post-transplantation (Parolari, et al., 2002). Prolonged ischemia time has been shown to be an important risk factor for early donor heart dysfunction and recipient death (Banner, et al., 2008; Russo, et al., 2010; Lund, et al., 2017). This causes transplanting physicians to only select donor hearts that they deem to be most likely able to withstand the potential injury associated with cold storage preservation, leaving most donor hearts unutilized annually.

Cold storage can only safely preserve a heart for about 4 hours, imposing significant time and geographical limitations on the heart retrieval process that further adversely impacts the utilization of available donor hearts. In an analysis of UNOS data, Russo, et al. (2007) showed the impact on survival of recipients of donor hearts with extended ischemic times, particularly when limited to donors ages 34 and older (note that the mean age of donors in the OCS Heart EXPAND trial was 37). One-year survival for recipients of donor hearts preserved for 3.5 to 5.49 hours was 81%, and survival for recipients of donor hearts preserved for greater than 5.5 hours was 68.5% (Figure 12).

Figure 12: Kaplan-Meier Analysis of UNOS Data for Heart Transplant Recipients of Donors Age ≥ 34 with Limited, Prolonged and Extended Ischemic Times (Figure 1C from Russo, et al., 2007)



Finally, cold storage lacks any ability to optimize or resuscitate donor hearts from the negative environment of brain death and does not allow the physician the opportunity to assess donor heart function during preservation and prior to transplant. The above complex constellation of the limitations of cold storage applies pressure on the clinical decision-making ability of whether to accept a donor heart for transplantation. The limitations ultimately result in the significant underutilization of donor hearts from brain dead donors (DBD) and the lack of utilization of any donor heart from donation after circulatory death (DCD) donors.

These challenges represent a significant unmet clinical need for new technologies that can address the limitations of cold storage and allow for better preservation and assessment of donor hearts to maximize donor heart utilization for transplantation.

The OCS Heart System was developed to comprehensively address the major limitations of cold storage that impact donor heart utilization. The OCS is a portable extracorporeal organ perfusion, optimization and monitoring system that replicates near-physiologic conditions for donor hearts outside of the human body. The OCS Heart System perfuses donor hearts with warm, oxygenated, nutrient-enriched blood, while maintaining the hearts in a beating, functioning state. Specifically, the OCS Heart System offers the following potential advantages and capabilities:

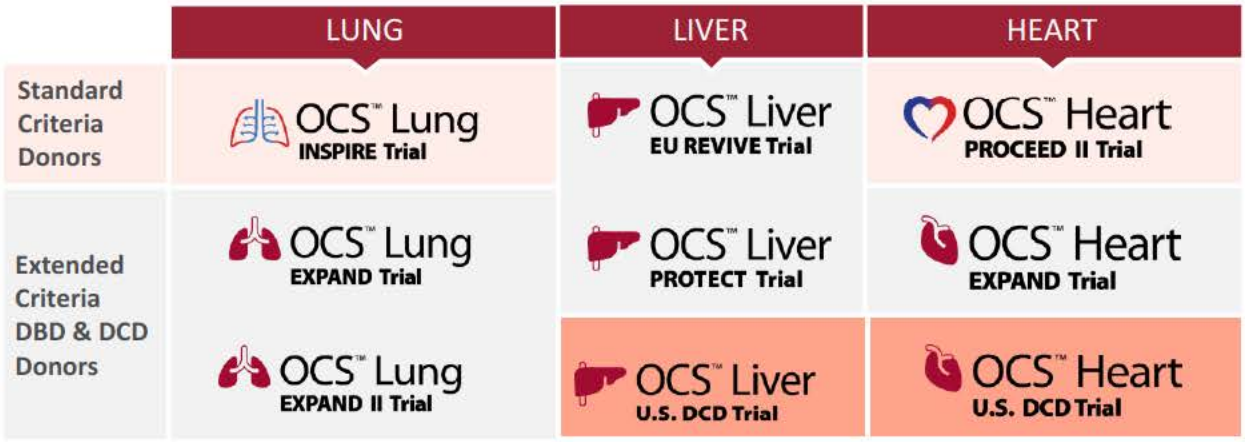
- Reduction of time-dependent ischemic injury to the donor heart during preservation, which could address the existing logistical and geographical barriers to heart transplantation that currently exist with cold storage preservation.
- Optimization of the donor heart ex-vivo environment by optimizing oxygen and substrate delivery, while also replenishing nutrients and hormones that are depleted due to the brain death insult, which could negatively impact cardiac function if not replenished.
- Resuscitation of the donor heart into a beating near-physiologic state ex-vivo to enable the assessment of the donor heart's viability for transplantation.
- Assessing the adequacy of the perfusion and metabolic condition of the donor heart utilizing circulating lactate trends, and other OCS hemodynamics to allow physicians to evaluate the suitability of the organ for transplantation, thus minimizing the risk of transplanting poorly functioning hearts into recipients.

3. COMPANY AND DEVICE BACKGROUND

TransMedics, Inc. (hereafter, "TransMedics") has designed, developed, tested, and marketed a platform for the *ex-vivo* perfusion of solid organs for transplantation. The platform can address the needs of different solid organs by incorporating a disposable perfusion module designed specifically for each organ. TransMedics has a comprehensive device development program (Figure 13) for use of the device in standard and extended criteria hearts, lungs, and livers, including DCD organs, which includes:

- OCS Lung System which has secured FDA PMA approval for both standard criteria donor lungs, as well as extended DBD and DCD donor lungs that initially were deemed unacceptable for transplantation based on limitations of cold storage.
- OCS Liver System for which a PMA has been submitted for DBD and DCD donor livers.
- OCS Heart System: this PMA ((b)(4)) which is under review and is the focus of this panel meeting.

Figure 13: Clinical Development Programs for OCS Technology



A more detailed summary of the development and FDA status of the various OCS Systems is shown in Table 4 below.

Table 4: Summary of OCS Platforms under Development in the U.S. and their Status

FDA Submission	Device	Organ	Overview	Current Status
P160013	OCS Lung	Standard Donor Lungs	Original PMA Submission for OCS Lung System, included pivotal clinical trial for the OCS for the preservation of standard donor lungs compared to cold storage preservation	FDA Approved on March 22, 2018
P160013	OCS Lung	Donor Lungs initially deemed unacceptable for transplant (including DCD Lungs)	Pivotal clinical trial for the OCS for the preservation of certain donor lungs that do not meet the standard criteria for donation as described in the protocol	FDA Approved on May 31, 2019
(b)(4) G140111	OCS Heart	Extended criteria - DBD donor hearts that are seldom transplanted today due to limitations of cold storage	Original PMA application for OCS Heart System	Under review by FDA and subject of this panel meeting
G140111/S029	OCS Heart	Extended criteria - DBD donor hearts that are seldom transplanted today due to limitations of cold storage	Continued Access Protocol (CAP) for the Heart EXPAND trial	Currently enrolling
G180272	OCS Heart	DCD donor hearts	Pivotal trial to demonstrate safety and effectiveness of	Enrollment completed and trial is in follow-up

FDA Submission	Device	Organ	Overview	Current Status
			OCS Heart to resuscitate, preserve and assess DCD hearts for transplantation	phase, received FDA Breakthrough Device status for this trial
G060127	OCS Heart	Standard Donor Hearts	First clinical study of OCS Heart System & first clinical trial of any OCS Technology	Referenced in this PMA submission as additional data
G140192	OCS Liver	Standard and Non-Ideal Donor Livers	Randomized, controlled pivotal trial of the OCS Liver System compared to standard of care cold storage preservation	Completed enrollment of 300 subjects, PMA submitted and under review by FDA
(b)(4)	OCS Liver	DCD donor Livers with extended warm ischemia time or older donors, those rarely transplanted today	Pivotal trial to demonstrate the safety and effectiveness of OCS Liver to preserve and assess DCD livers that are rarely transplanted today	Currently being initiated, received FDA Breakthrough Device status for this trial

Note: In describing the regulatory history of the OCS Heart System in their Panel Executive Summary, FDA has cited "Study Design Considerations" that were communicated in IDE correspondence. These were recommendations and were not requirements and FDA approved the IDEs for both the OCS Heart EXPAND trial and associated CAP. Importantly, TransMedics had responded to all Study Design Considerations, and we made changes or adjustments to the protocol as needed. In situations where we disagreed with FDA's recommendation, we provided our detailed clinical rationales to FDA. (b)(4)

4. DEVICE DESCRIPTION – OCS HEART SYSTEM

The OCS Heart System consists of:

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

The current version of the OCS Heart System consists of Heart Console 1.6, Software 3.3.7-C, HPS 1.4, and OCS Heart Solution Set 1.5.

4.1. Heart Console

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

4.2. Heart Perfusion Set (HPS)

The HPS consists of the HPM and the disposable HPS Accessories. The HPM provides a closed circulatory system to protect, maintain, and support the heart. It uses a physical conduit to connect to the heart, incorporates various sensors, and interfaces with the Heart Console to oxygenate, warm, and circulate the perfusate.

The accessories are intended to:

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

The HPM provides the sterile blood circuit and protected environment for a heart within the OCS Heart System. It is designed as a single-use, pre-assembled module that mounts into the Heart Console. Once the system is primed and prepared, the heart is instrumented within the heart chamber of the HPM. The Wireless Monitor displays measurements made within the HPM. The HPM includes:

- Clamshell-shaped, heart-specific polycarbonate chamber
- Integrated and easily accessible blood sampling and de-airing manifold
- Integrated pulsatile pump head interface
- Integrated low-shear titanium blood warmer
- Integrated blood oxygenator (i.e., gas exchanger)
- Integrated sensors (ECG, pressure, and temperature) and circuitry to communicate with the Heart Console.

4.3. OCS Heart Solution Set

The OCS Heart Solution Set consists of two proprietary heart preservation solutions, the OCS Priming Solution and the OCS Maintenance Solution, to replenish the nutrients and hormones that the metabolically active donor heart requires (Table 5). The solutions are packaged in a three-chamber bag (nominal volume of 500 mL per chamber). At the time of use, the OCS Priming Solution (500 mL) is dispensed into the HPM. The OCS Maintenance Solution is manufactured as two-component solutions (500 ml each) that are individually manufactured and then mixed immediately before infusion into the HPM. Additives are required at the time of use that are supplied and added by the user.

The OCS Heart Solution Set is not intended to be administered directly to the donor or the recipient. Prior to transplantation into the recipient, the donor heart is arrested on the OCS through the use of mechanical cooling and administration of a cardioplegia solution, at which time the perfusate (including the donor blood, OCS Priming Solution and OCS Maintenance Solution) is flushed from the donor heart.

Table 5: Chemical Composition of the OCS Priming and Maintenance Solutions

Substance	Purpose
OCS Priming Solution[1]	
Mannitol	Osmotic pressure
Sodium Chloride	Electrolyte balance
Sodium Glycerophosphate	Phosphate Source for metabolic balance
Potassium Chloride	Electrolyte balance
Magnesium sulfate heptahydrate	Electrolyte balance
Hydrochloric Acid	pH adjustment during manufacturing
Water for Injection	Fluid
OCS Maintenance Solution[2]	
Calcium Chloride (g)	Electrolyte to support metabolism
Magnesium Sulfate (g)	Electrolyte to support metabolism
Potassium Chloride (g)	Electrolyte to support metabolism
Sodium Chloride (g)	Electrolyte to support metabolism
Adenosine (g)	Nutrient to support metabolism
Dextrose (g)	Energy Source
Amino Acids	Nutrients to support metabolism

[1] OCS Priming Solution of 500 mL to prime the OCS circuit.

[2] This is the composition after the two separate OCS Maintenance Solution chambers are mixed.

The operation of the OCS Heart System requires the user to supply certain additives, which are listed in Table 6 below.

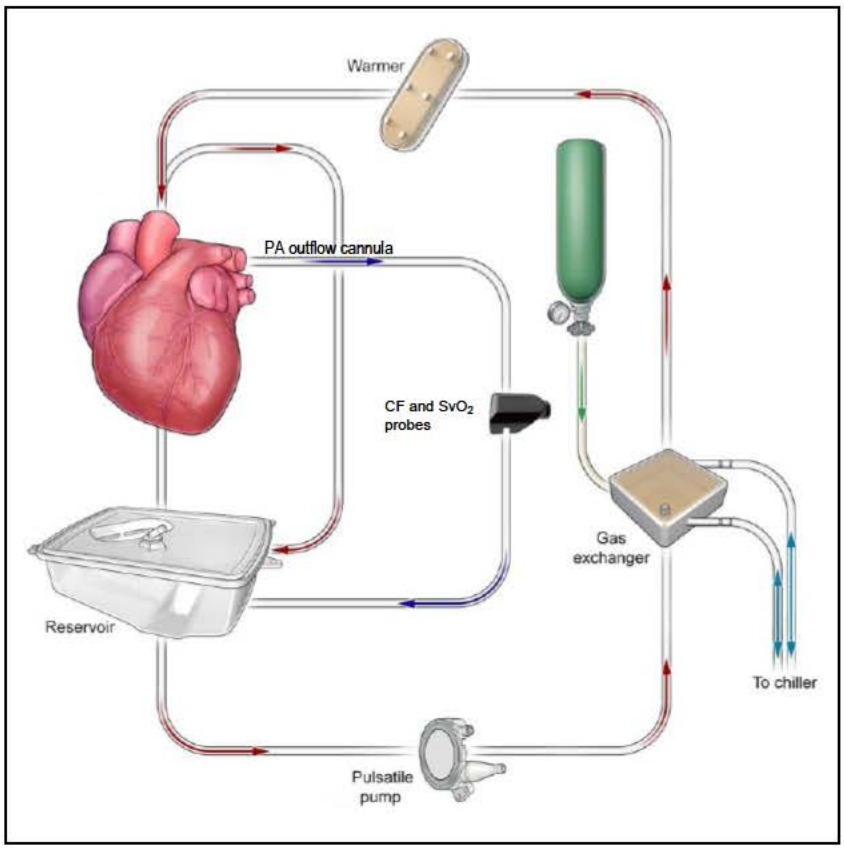
Table 6: Additives to OCS Heart Solutions Supplied by User

Substance	Purpose
Sodium Bicarbonate	Buffer
Heparin	Anti-coagulant
Methylprednisolone	Anti-inflammatory
Multivitamins	Nutrient to support metabolism
Ciprofloxacin or Equivalent Gram-Negative Antibiotic	Antibiotic
Cefazolin or Equivalent Gram-Positive Antibiotic	Antibiotic
Human albumin	Oncotic pressure
Regular Insulin	Support metabolism
Epinephrine 0.25mg in 500 mL of Dextrose 5% solution, plus Regular Insulin	Replenish depleted catecholamines ex-vivo

4.4. Mode of Action

The OCS Heart System preserves the heart in a near-physiological, beating state by perfusing the heart with a warmed, donor-blood based solution that is supplemented with nutrients and oxygen in a controlled and protected environment, referred to as the circuit. The circuit is illustrated in Figure 14 below. The OCS contains a pulsatile pump that directs flow through the gas exchanger to infuse oxygen, then through the blood warmer, and then to the aorta of the donor heart. The OCS Maintenance Solution is infused into this circuit. The heart consumes oxygen and nutrients as the blood travels from the aorta through the coronary arteries and returns blood to the circuit through its pulmonary artery. The OCS maintains the blood at a constant temperature, oxygenates the perfusate, and provides perfusate in a pulsatile flow.

Figure 14: Schematic of the OCS Fluid Flow



To adequately perfuse the heart, the OCS Heart System controls and monitors the preservation environment (Table 7). The user can adjust blood flow rate, solution delivery rate, gas flow rate, and blood temperature within specified ranges, all of which contribute to the ability to adequately perfuse the donor heart. The OCS calculates and displays pertinent organ perfusion parameters, and provides alarms for parameters out of expected ranges, alarms for low gas and battery capacity, and alarms for sensor failures.

Table 7: Essential Control and Monitoring of the Preservation Environment

Function	Mechanism	Measurement	User Control
Circulate Perfusate	Blood Pump	Flow Rate	Pump Flow Rate
		Pressure	
Warm Perfusate	Warmer Titanium Plates	Blood Temperature	Blood Temperature
		Plate Temperature	
Replenish Perfusate	Gas Supply	Oxygen Saturation	Gas Flow Rate
	Solution Delivery	Parameters (flow rates, pressures)	Solution Delivery Flow Rate

Circulate Perfusate: The OCS Heart System controls rate of perfusate flow and the rate of delivery of the OCS Maintenance Solution to replenish nutrients consumed by the beating heart. The OCS contains multiple flow probes and multiple pressure transducers to measure flow and pressure, respectively, and to avoid a single point failure. The OCS alerts the user to faults or parameter values outside of the specified ranges.

Warm Perfusate: The OCS Heart System warms the perfusate using redundant warmer titanium plates and measures perfusate temperature through redundant sensors. The OCS displays the blood temperature value and alerts the user to faults or parameter values outside of specified ranges. The recommended temperature setting is 34°C.

Provide Oxygen: The OCS Heart System provides oxygenated gas to the circuit. The system displays oxygenation values and alerts the user to faults or parameter values outside of specified ranges.

Assess Preservation: In addition to the heart preservation capability, the OCS Heart System was specifically designed to provide a means to allow the transplantation team to evaluate the preservation conditions and the function of the organ during transport. The OCS Heart System monitors the preservation conditions by measuring flow rates, pressures, temperature, circulating blood oxygen saturation and heart rate of the donor heart. The circuit contains ports to draw blood samples for analysis of blood gas and circulating metabolites (e.g., lactate level) without disrupting sterility. Preservation parameters are displayed to the user and stored in the system.

4.5. Principles of Operation/Clinical Use

Principles of the operation and specifics regarding clinical use of the OCS Heart System are summarized in Appendix 1 of this document.

5. SUMMARY OF NON-CLINICAL STUDIES

TransMedics has performed an extensive number of non-clinical studies to demonstrate that the OCS Heart System performs as intended, meets its performance specifications, and is safe for its intended use. The completed verification and validation tests demonstrate that the device performs as intended, and that risks to patients and health care providers have been minimized. A summary of the non-clinical studies performed on the OCS Heart System is provided in Appendix 2 of this document.

6. CLINICAL DATA SUPPORTING THE OCS HEART SYSTEM PMA

The primary clinical data set supporting this PMA application is the OCS Heart EXPAND trial and the OCS Heart EXPAND CAP. The following sections describe the OCS Heart EXPAND trial and results, followed by the pooled analysis of the OCS Heart EXPAND trial and the OCS Heart EXPAND CAP trials. Additional data included in this PMA are the PROCEED II trial and published long-term international studies of the OCS Heart System for standard criteria, extended criteria, and DCD hearts.

6.1. OCS Heart EXPAND Trial Design and Objectives

The primary data supporting this PMA for the OCS Heart System for the proposed indication for use is the OCS Heart EXPAND trial that was conducted under IDE G140111. This trial was conditionally approved by FDA on July 23, 2014, and fully approved on September 3, 2014.

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

To be clinically robust and maximize clinical value and safety for potential transplant recipients in this trial, TransMedics sought the advice and guidance of leading U.S. academic heart failure cardiologists and transplant surgeons to define the specific types of donor hearts to be used in the OCS Heart EXPAND protocol, which is reflected in the donor eligibility criteria for this trial.

6.1.1. Study Design

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

Designing this trial as a randomized controlled trial (RCT) was not feasible or ethical for the proposed indication, given the fact that donor hearts that were enrolled in the OCS Heart EXPAND trial are seldom used for transplantation today due to inherent limitations of ischemic cold storage. It would not be feasible or ethical to require that surgeons preserve these donor hearts on cold storage and it would have subjected potential recipients in the control arm to an unacceptably high risk of poor post-transplant outcomes, including death.

6.1.1.1. Primary Effectiveness Endpoint

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

6.1.1.2. Secondary Effectiveness Endpoints

- Patient survival at Day-30 post-transplantation.

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

6.1.1.3. Additional Clinically Relevant Analyses

Additional analyses include:

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

6.1.1.4. Safety Endpoint

Incidence of Heart Graft-related Serious Adverse Events (HGRSAEs) in the first 30 days post heart transplantation, defined as:

- Moderate or severe PGD (left or right ventricle) (not including rejection or cardiac tamponade), as defined in Appendix 2 of the protocol according to ISHLT consensus manuscript (Kobashigawa, et al., 2014).
- Primary graft failure requiring re-transplantation.

It was not necessary to include a statistically driven safety endpoint in the OCS Heart EXPAND trial, since the primary endpoint already incorporated the most clinically relevant safety outcomes, i.e., PGD and patient survival.

6.1.2. Trial Population

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

6.1.3. Inclusion Criteria

Donor: At least one of the following:

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

- History of Carbon monoxide poisoning with good cardiac function at time of donor assessment; or
- Social history of alcoholism with good cardiac function at time of donor assessment; or
- History of diabetes combined with negative coronary angiogram for coronary artery disease (CAD).

Recipient - Day of Transplant

- Registered male or female primary heart transplant candidate and
- Age ≥ 18 years old and
- Signed: (1) written informed consent document and (2) authorization to use and disclose protected health information.

6.1.4. Exclusion Criteria

Donor

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

Recipient - Day of Transplant

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

6.1.5. Donor Heart on OCS Acceptance Criteria

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

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

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

This relationship between rising lactate levels in OCS Heart perfusate and post-transplant graft failure or dysfunction was established in a prospective analysis of the early global OCS experience (n=49 patients transplanted with OCS perfused donor hearts). In this study, 49 patients transplanted with perfused donor hearts were analyzed in logistic regression analyses. Graft failure within 30 days as the outcome variable and a variety of predictor variables were explored (i.e., ending lactate, rise of lactate change, ending venous-arterial difference, CF, cardioplegia solution, and AOP). The results demonstrated that ending arterial lactate level on OCS was statistically significant in all models ($p \leq 0.01$) and at a cut-off of 4.96 mmol/L, the sensitivity was 0.625 and the specificity was 0.975. This analysis that validated the use of lactate was presented at the ISHLT meeting in 2009, and the abstract was published in the Journal of Heart and Lung Transplantation (Hamed, et al., 2009). The above data formed the basis for establishing the cutoff range of acceptable end of perfusion arterial lactate level on OCS at < 5 mmol/L. Ever since, the measurement of lactate has been a guiding principle in managing a donor heart on OCS in addition to overall clinical judgment based on heart contractility and perfusion parameters. This principle was incorporated into the OCS Heart EXPAND trial and all OCS Heart commercial use outside the U.S.

6.1.6. Analysis Populations

The transplanted recipient population consisted of all recipients who were transplanted according to the protocol and who had no major protocol violations. The analyses of all effectiveness and safety endpoints, except the rate of donor heart utilization, was based on the transplanted recipient population. In this trial, there were no major protocol violations, so all recipients transplanted with hearts preserved on OCS were included in the transplanted recipient population.

The OCS heart population consisted of all donor hearts that were instrumented on the OCS Heart System. The analysis of the rate of donor hearts utilization was based on the OCS heart population.

6.1.7. Statistical Analyses

6.1.7.1. Sample Size

The sample size for this trial was determined based on the primary effectiveness endpoint. The calculation assumed a one-sided exact binomial test, an alpha level of 0.05, a Performance Goal of 0.65, a true survival rate for OCS of 0.8, and power of 80%. Based on these specifications, the required sample size was determined to be 55 transplanted recipients. The sample size was increased to 75 to increase statistical power to examine the site effects, as well as the effect of other covariates.

6.1.7.2. Statistical Analyses – Effectiveness

The primary hypothesis was that the true proportion of transplanted recipients with composite patient survival at Day 30 post-transplantation and absence of severe ISHLT PGD (left or right ventricle) in the first 24 hours post-transplantation was greater than the Performance Goal value of 0.65 using a one-sided exact binomial test at the 0.05 significance level. The primary

effectiveness endpoint was summarized using counts and percentages and an exact 95% confidence interval for the true percentage based on the binomial distribution.

For the primary effectiveness endpoint, a site effect analysis was conducted to assess the poolability of data across clinical sites. For this analysis, sites with fewer than five subjects were grouped into a single, larger analysis site. A 0.15 significance level was used for this test. The p-value was 0.8784; therefore, no adjustment for site was needed.

Each secondary effectiveness endpoint was summarized using counts and percentages and an exact 95% confidence interval for the true percentage based on the binomial distribution. No formal hypothesis tests were conducted.

Survival analyses were performed using the Kaplan-Meier method.

6.1.7.3. Statistical Analyses – Safety

For the primary safety endpoint, the number of HGRSAEs up to the 30-day follow-up after transplantation per subject was analyzed. This endpoint was summarized using the mean, median, standard deviation, minimum, maximum, and a 95% confidence interval for the mean based on the t-distribution.

6.1.8. Investigators and Study Administrative Structure

Table 8: Study Administrative Structure - Oversight Personnel

Function	Name	Role/Affiliation
Product Director	(b)(6)	Sponsor/TransMedics, Inc.
Project Manager	(b)(6)	Sponsor/TransMedics, Inc.
Chief Medical Officer	(b)(6)	Sponsor/TransMedics, Inc.
VP, Global Regulatory Affairs	(b)(6)	Sponsor/TransMedics, Inc.
Statistical Consultant	(b)(6)	Independent Biostatisticians (b)(6)
Independent Medical Monitor	(b)(6)	Lung & Heart Transplant Surgeon/(b)(6)
Data Safety Monitoring Board	(b)(6)	Chairperson (b)(6)
	(b)(6)	Biostatistician Professor of Mathematics and Statistics, Biostatistics and Epidemiology (b)(6)
	(b)(6)	Cardiac Transplantation (b)(6)

Table 9: Study Site Principal Investigators (PIs)

PI Name	Investigational Sites	Transplanted Recipients
(b)(6)	(b) (6)	29
(b)(6)	(b) (6)	13
(b)(6)	(b) (6)	12
(b)(6)	(b) (6)	7
(b)(6) (b)(6) (b)(6)	(b) (6)	7
(b)(6)	(b) (6)	3
(b)(6)	(b) (6)	2
(b)(6) (b)(6)	(b) (6)	1
(b)(6)	(b) (6)	1
TOTAL OCS Heart EXPAND Trial Transplanted Patients		75

An Independent Core Pathology Laboratory reviewed heart biopsy samples for the turned down donor hearts. Table 10 below identifies the Core Pathology Laboratory and independent pathologist.

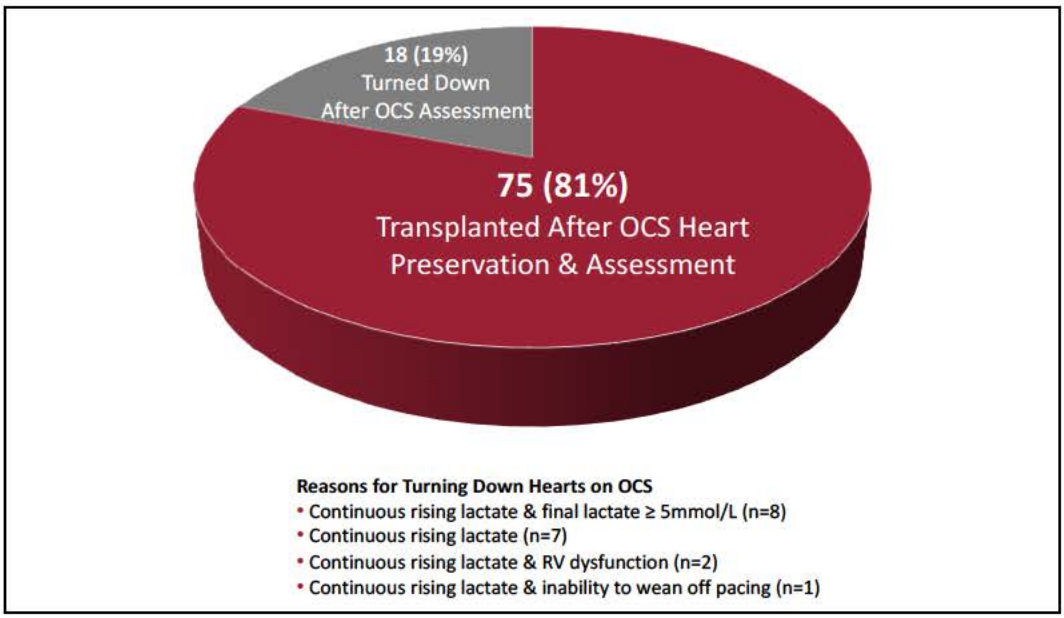
Table 10: Independent Core Pathology Laboratory

Name	Affiliation	Function	Specialty
(b)(6)	(b) (6)	Core Lab Pathologist	Cardiology/ Pathology
(b)(6) (b)(6)	(b) (6) (b)(6)	Core Lab Pathologist	Pathology

6.1.9. Donor Heart Disposition

In the OCS Heart EXPAND trial, a total of 93 donor hearts were preserved and assessed on OCS and of these, 75 were transplanted, giving a utilization rate (as defined in the protocol) of 81% (see Figure 15).

Figure 15: OCS Heart EXPAND Trial Donor Utilization



This is a clinically important result, given that donor hearts were rejected by other centers and likely would not have been utilized outside of the OCS Heart EXPAND trial. Table 11 below shows the donor match run data available from UNOS for the 93 donor hearts preserved on the OCS Heart System for the OCS Heart EXPAND trial. These 93 hearts were refused for transplant by other centers an average of 66 times (median 29) before acceptance into the OCS Heart EXPAND trial. For reference, from 2007-2014, the median number of refusals for heart transplants in the U.S. was 2 (Baran, et al., 2019), which further suggests that the donor hearts transplanted in the OCS Heart EXPAND trial would likely have gone unutilized outside of the trial.

Table 11: Donor Heart Offers Refusals Prior to Acceptance in OCS Heart EXPAND Trial

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

6.1.10. OCS Heart EXPAND Trial Recipients Enrollment

There were 96 patients who signed informed consent with data in the database. Of these, 6 patients were not matched with a donor heart that was instrumented on the OCS:

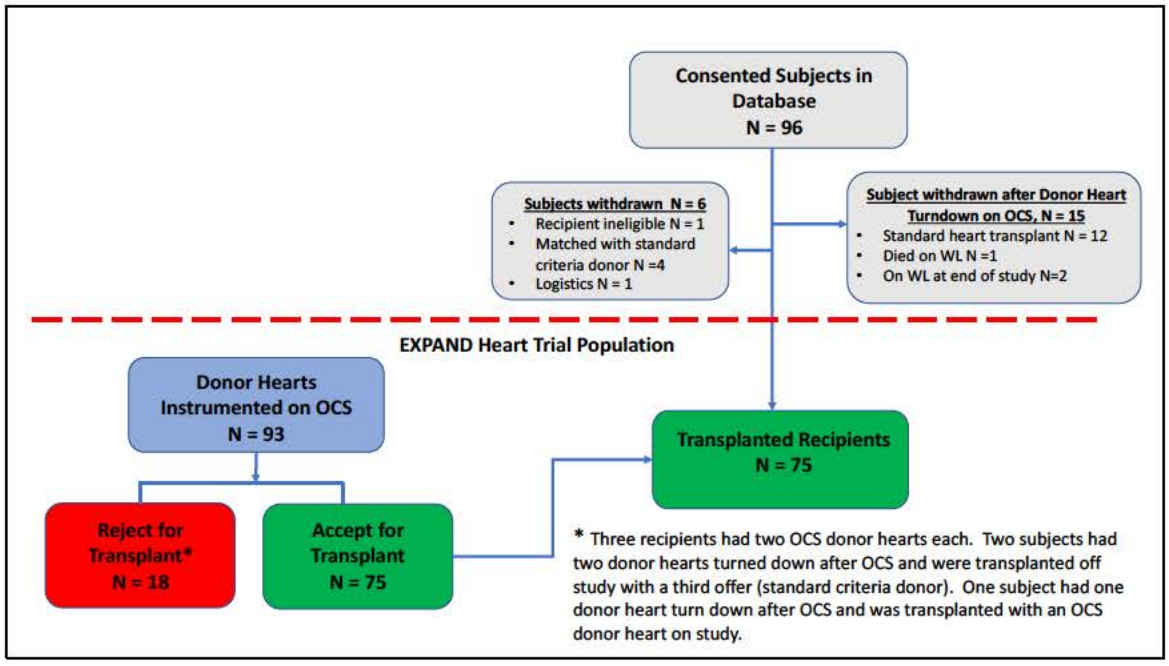
- 4 patients were matched with a standard criteria donor heart
- 1 patient became ineligible (delisted for transplant)
- 1 patient was withdrawn and transplanted with a donor heart preserved on ice due to logistics.

Sixteen (16) patients were matched with donor hearts that were turned down following OCS preservation and assessment. The disposition of these 16 patients was as follows:

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

Therefore, the transplanted recipient population consists of 75 patients who were transplanted with donor hearts preserved and assessed on the OCS Heart System. The analyses of all effectiveness and safety endpoints were based on the transplanted recipient population. The OCS Heart EXPAND transplanted recipient population is illustrated in Figure 16 below.

Figure 16: OCS Heart EXPAND Heart Trial Population



NOTE: In their Panel Executive Summary, FDA has asserted that there are "missing" data in this PMA. The FDA assertions are based on the subjects who were withdrawn and transplanted off-trial with a standard criteria donor heart preserved on cold storage or who died on the waiting list awaiting a donor heart offer or were not transplanted at all during the EXPAND trial (indicated in gray boxes in Figure 16 above). Outcomes of these patients are not clinically relevant to the assessment of the OCS Heart System's safety and effectiveness given that OCS was not used for these patients. In addition, the OCS Heart EXPAND trial protocol did not specify data collection for screen failures. The data in this PMA include outcomes for all subjects transplanted with OCS preserved donor hearts, and all donor hearts that were instrumented on OCS (either transplanted or turned down). Therefore, we acknowledge FDA's position about patients who were transplanted with a standard criteria donor heart outside of the study, but we respectfully disagree with FDA's assessment that these data are "missing" in the EXPAND trial analyses.

6.1.11. Recipients Demographic Characteristics and Risk Factors

The recipient demographics are shown in Table 12 below. The majority of recipients (69%) were status 1A and were on mechanical circulatory support at the time of transplant (64%). Recipient characteristics are also presented by known risk factors for heart transplant recipients (Sorabella, et al., 2015; Trivedi, et al., 2016).

Table 12: Recipient Demographics in OCS Heart EXPAND Trial

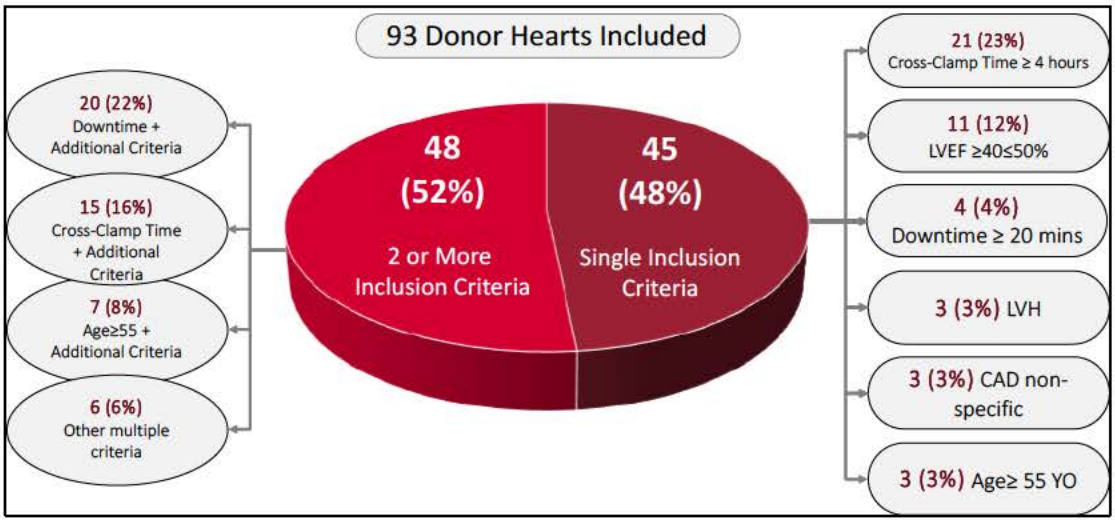
Recipient Characteristics	OCS Transplanted Recipients N=75
Age (years) mean ± SD	55.5 ± 12.6
Age > 65	18 (24.0%)
Gender – male n (%)	61 (81.3 %)
BMI (kg/m^2) – mean ± SD	27.7 ± 4.7
Race	
• Asian	2 (2.7%)
• Black or African American	12 (16.0%)
• White	58 (77.3%)
• Other	2 (2.7%)
• Not Provided	1 (1.3%)
History of Mechanical Circulatory Support	48 (64.0%)
• LVAD	47 (62.7%)
• RVAD	0 (0%)

Recipient Characteristics	OCS Transplanted Recipients N=75
• BiVAD	1 (1.3%)
• ECMO	0 (0%)
Status n (%):	
• Status IA	52 (69.3%)
• Status IB	22 (29.3%)
• Status II	1 (1.3%)
Primary Etiology of Heart Failure Diagnosis	
• Ischemic Cardiomyopathy	26 (34.7%)
• Congenital Heart Disease	2 (2.7%)
• Restrictive Cardiomyopathy	7 (9.3%)
• Non-ischemic Cardiomyopathy	24 (32.0%)
• Dilated Cardiomyopathy	9 (12.0%)
• Other	7 (9.3%)
Female donor to male recipient mismatch	12 (16.0%)
Renal dysfunction	11 (14.7%)
PRA (%) mean (range)	7.9 (0-81)

6.1.12. Donor Risk Factors

This trial enrolled a very complex group of donor hearts with many exhibiting multiple risk factors and inclusion criteria. To illustrate this complex nature of the multiple criteria donor hearts enrolled in the OCS Heart EXPAND trial, Figure 17 below shows the detailed inclusion criteria for all 93 donor hearts that were enrolled and assessed on the OCS Heart System.

Figure 17: Characteristics of All Donor Hearts in OCS Heart EXPAND Trial Meeting One, Two or More Inclusion Criteria*



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

This complex donor criteria were also reflected in the donors that were transplanted in the OCS Heart EXPAND trial (Table 13). Thirty-five (35) of the 75 transplanted donor hearts (47%) met more than one inclusion criterion.

Table 13: Donor Inclusion Criteria Met for Transplanted Donor Hearts in the OCS Heart EXPAND Trial*

Parameter	OCS Transplanted Donors N=75
Donor Inclusion Criteria Met n (%)	
Expected Cross-Clamp Time ≥4hr	28 (37.3%)
Donor Age ≥ 55	10 (13.3%)
LVH	17 (22.7%)
Downtime ≥ 20 min	23 (30.7%)
LVEF 40% -50%	21 (28.0%)
Luminal irregularities	7 (9.3%)
Alcoholism	9 (12.0%)
Carbon Monoxide as cause of death	1 (1.3%)
Diabetes	2 (2.7%)
Donor Age 45-55 with no coronary cath data	1 (1.3%)
Donors with Multiple Criteria	35/75 (46.7%)

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

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

FDA's Panel Executive Summary has questioned whether the donor hearts in the OCS Heart EXPAND trial are "extended criteria" and has asserted that the donor hearts in the OCS Heart EXPAND trial are "generally clinically similar to the donors in PROCEED II."

TransMedics has taken this issue seriously and we consulted with our investigators and key opinion leaders to determine how to best address FDA's assertion that the donor hearts in EXPAND are no different from standard criteria donor hearts routinely transplanted today in the U.S. We collectively believe that this issue is best addressed by examining data from the national UNOS/SRTR database of standard criteria donors transplanted today using cold storage.

The analysis utilized de-identified data from the UNOS/SRTR database, which included all heart transplant recipients in the U.S. from January 2015 through December 2018 (i.e., the years that Heart EXPAND was conducted). This is an analysis of donor characteristics/risk factors only and does not include post-transplant outcomes.

The UNOS/SRTR cohort includes 10,426 adult heart transplants, and it excludes any transplants in the OCS Heart EXPAND trial. It is important to note that, in this analysis, we were only able to evaluate donor risk factors that are collected in the UNOS/SRTR database. Some of the OCS Heart EXPAND donor characteristics/risk factors are not captured in the UNOS/SRTR database, such as LVH and coronary artery luminal irregularities, since they are historically considered to be major risk factors for heart donation and these hearts are seldomly used for transplantation. Therefore, the analysis assessed the available donor characteristics/risk factors for the N=10,426 donor hearts in the UNOS/SRTR cohort and compared them to the same risk factors in the N=93 donor hearts in the OCS Heart EXPAND trial (see Table 14 below).

Of the 10,426 donor hearts preserved on cold storage in 2015-2018, the UNOS/SRTR data indicated that:

- Only 2% of the donor hearts had downtime ≥20 minutes
- Only 3% of the donor hearts had donor age ≥ 55
- Only 5% of the donor hearts had LVEF 40-50%
- Only 4% of the donor hearts had a history of diabetes
- Only 15% of the donor hearts had cross-clamp time ≥ 4 hr
- Only 17% of the donor hearts had a history of alcoholism.

The data demonstrate that the EXPAND donors are not routinely transplanted on cold storage in the U.S. today. This is further demonstrated when considering donors transplanted in the U.S. on cold storage with two or more donor inclusion criteria (which comprised 52% of the donor hearts in the OCS Heart EXPAND trial). As shown in Table 14 below, of the 10,426 donor hearts preserved on cold storage in 2015-2018:

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

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

These data, in conjunction with the UNOS donor match run data described in Table 11, show that the donor hearts preserved on OCS in the OCS Heart EXPAND trial are not routinely transplanted today, and this is an important clinical consideration in the assessment of the benefits and risks of the OCS Heart System to increase the number of successful heart transplants in the U.S.

Table 14: Donor Characteristics for EXPAND vs. UNOS/SRTR Hearts transplanted 2015-2018

Donor Characteristics	Expand OCS (N=93)	SRTR (N=10,426)	p-value
Age (yr) – Mean ± SD	36.3 ± 13.1	32.0 ± 11.0	0.0022
Age ≥ 55 - n (%)	11 (11.8%)	295 (2.8%)	<0.0001
LV Ejection Fraction % - Mean ± SD	57.4 ± 8.7	61.7 ± 6.5	<0.0001
Cross-Clamp Time ≥ 4 Hours – n (%) (Expected)	37 (39.8%)	1607 (15.4%)	<0.0001
Cross-Clamp Time ≥ 4 Hours – n (%) (Actual)	72 (96.0%)	1607 (15.4%)	<0.0001
LVEF between 40% - 50% - n (%)	24 (25.8%)	481 (4.6%)	<0.0001
Down Time ≥ 20 Minutes – n (%)	33 (35.5%)	240 (2.3%)	<0.0001
Social History of Alcoholism – n (%)	10 (10.8%)	1756 (16.8%)	0.1266
History of Diabetes - n (%)	3 (3.2%)	383 (3.7%)	1.0000
a. Cross-Clamp Time ≥ 4 h and (Age (yr) ≥ 55 or Downtime ≥ 20 Min. or History of Alcoholism or History of Diabetes or LVEF 40-50%) – n (%)	13 (14.0%)	464 (4.5%)	0.0003
b. Age (yr) ≥ 55 and (Downtime ≥ 20 Min. or History of Alcoholism or History of Diabetes or LVEF 40-50%) – n (%)	7 (7.5%)	104 (1.0%)	<0.0001
c. Downtime ≥ 20 Min. and (History of Alcoholism or History of Diabetes or LVEF 40-50%) – n (%)	9 (9.7%)	58 (0.6%)	<0.0001

6.1.14. Transplanted Donor Heart demographic information

Table 15 below shows the donor demographic information broken down by donor inclusion criteria for the transplanted donor hearts, as well as for the entire transplanted donor population.

Table 15: Donor Demographics by Inclusion Criteria and for All Donors

	Diabetes + negative for CAD N=2	Alcoholism N=9	Carbon monoxide poisoning N=1	Luminal irregularity N=7	LVEF ≥ 40% and ≤ 50% N=21	Downtime ≥ 20 mins N=23	LVH N=17	Donor Age ≥ 55 yrs N=10	Donor 45-55 yrs w/ no coronary cath data N=1	Expected Cross-clamp Time ≥ 4 hours N=28	ALL Donors N=75
Cross-clamp Time (min) Mean ± SD	292.5 ± 9.2	400.2 ± 78.1	406	398.4 ± 140.1	354.7 ± 83.4	356.0 ± 77.0	360.1 ± 86.3	341.4 ± 48.0	431	429.3 ± 96.0	380.7 ± 93.2
Donor Age (yr) Mean ± SD	48.86	45.8 ± 11.8	35.3	48.8 ± 8.8	30.2 ± 9.5	34.1 ± 11.1	42.2 ± 12.7	56.1 ± 1.0	47.6	35.8 ± 12.5	37.3 ± 12.6
LV Septal wall thickness (mm), N Mean ± SD	2 10.0	9 10.3 ± 2.4	1 8.0	6 12.0 ± 2.5	18 9.9 ± 2.1	20 10.7 ± 2.5	17 12.5 ± 1.6	10 10.2 ± 2.1	1 8.0	20 9.0 ± 1.9	63 10.0 ± 2.3
Downtime (min), N Mean ± SD	--	3 12.7 ± 9.5	--	4 35.0 ± 20.4	9 37.2 ± 34.3	20 43.8 ± 30.9	12 35.0 ± 30.1	2 31.0 ± 41.0	--	6 34.7 ± 50.3	31 32.0 ± 29.5
LVEF (%), N Mean ± SD	2 52.5 ± 17.7	9 61.4 ± 8.4	1 60.0	7 59.3 ± 4.5	21 46.5 ± 3.7	23 57.1 ± 7.9	17 61.4 ± 6.2	10 61.0 ± 5.7	1 55.0	27 60.6 ± 7.1	74 57.4 ± 8.7
Additional Donor Characteristics											
Male Sex N (%)											54 (72.0%)
BMI (kg/m^2)											26.8 ± 5.3
Cause of Death N (%) Anoxia Stroke Head Trauma Other											 28 (37.3%) 17 (22.7%) 25 (33.3%) 5 (6.7%)

6.1.15. Donor Heart Preservation Characteristics and Critical Times

Donor heart preservation characteristics are shown in Table 16 below. Note that total cross-clamp time (total out-of-body time) is the time from aortic cross-clamp application in the donor to the aortic-cross clamp removal in the recipient, while the total ischemic time is the time that donor hearts were ischemic without any oxygenated perfusion.

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

Table 16: Donor Heart Preservation Characteristics

Parameter	OCS Heart EXPAND (N=75)
Cross-clamp Time (mins)[1]	N = 75
Mean ± SD	380.7 ± 93.2
Median	369.0
Min.- Max.	173 - 682
Total Ischemic Time (mins)[2]	N = 75
Mean ± SD	102.1 ± 22.6
Median	98.0
Min.- Max.	65 - 168
OCS Perfusion Time (mins)	N = 75
Mean ± SD	278.6 ± 83.3
Median	276.0
Min.- Max.	100 - 532

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

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

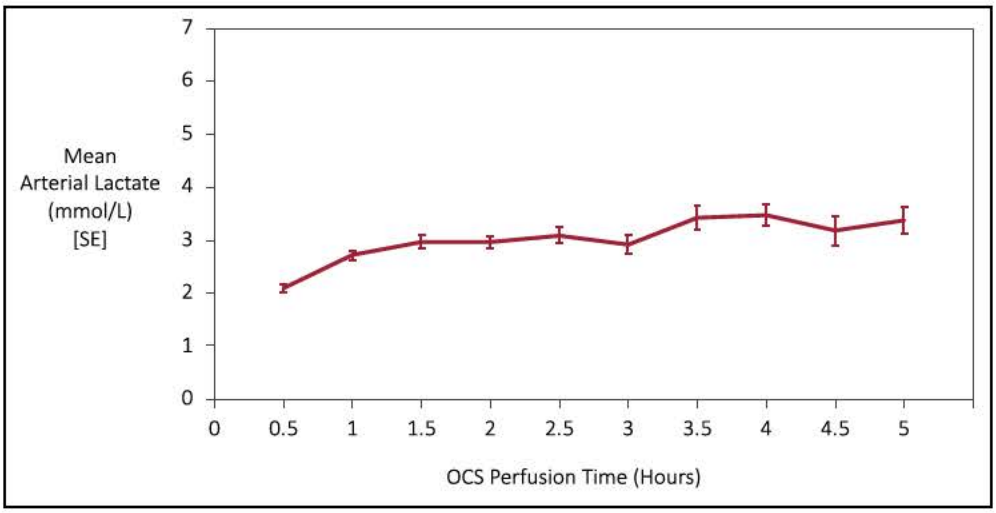
6.1.16. OCS Heart System Perfusion Parameters

The OCS Heart System perfusion parameters are summarized in Table 17 below. The donor hearts were maintained within the recommended parameters on the OCS Heart System.

Donor arterial baseline lactate level is a function of many different aspects of the donor demographics and retrieval environment and the lactate level in the donor is not optimized or controlled. Once the organ is placed on the OCS Heart System, the user has the ability to adjust the AOP and/or coronary flow to adequately perfuse the donor heart, resulting in a stable lactate profile. Further adjustments may then be made to maintain the lactate at acceptable

levels. Figure 18 below demonstrates the average lactate trend for all donor hearts on the OCS Heart System that were accepted for transplantation in the OCS Heart EXPAND trial.

Figure 18: Mean Lactate Levels During OCS Heart Perfusion for Donor Hearts Transplanted in EXPAND Trial



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

Table 17: OCS Heart System Perfusion Parameters

Parameter	OCS (N=75)
AOP Mean (mmHg)	N = 75
Mean ± SD	81.2 ± 7.8
Median	81.4
Min.- Max.	48 - 102
Coronary Flow (CF) (L/min)	N = 75
Mean ± SD	0.74 ± 0.13
Median	0.756
Min.- Max.	0.05 - 0.93
Arterial Lactate (mmol/L) – Initial OCS Instrumentation	N = 75

Parameter	OCS (N=75)
Mean ± SD	1.9 ± 0.63
Median	1.750
Min.- Max.	0.93 - 3.80
Arterial Lactate (mmol/L) – Final OCS Instrumentation	N = 75
Mean ± SD	3.08 ± 0.95
Median	3.01
Min.- Max.	0.55 - 4.97
Pump Flow (L/min)	N = 75
Mean ± SD	1.13 ± 0.12
Median	1.12
Min.- Max.	0.93 - 1.76
Heart Rate (BPM)	N = 75
Mean ± SD	78.8 ± 2.5
Median	78.6
Min.- Max.	74 - 87
Hematocrit (%)	N = 74
Mean ± SD	21.1 ± 3.6
Median	20.7
Min.- Max.	16 – 33.0

6.1.17. Primary Composite Effectiveness Endpoint

Table 18 below shows the results of the composite primary effectiveness endpoint. The primary effectiveness endpoint met the pre-specified objective performance goal of 65% (p <0.0001), and the results demonstrate that these extended criteria hearts, those seldom used for transplant today, can be transplanted successfully with favorable post-transplant outcomes.

Table 18: Primary Effectiveness Endpoint for OCS Heart EXPAND Trial

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

Results for Primary Endpoint Composite and Components	OCS (N=75)
p-value[3]	<0.0001

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

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

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

6.1.18. Secondary Effectiveness Endpoints

The secondary endpoints were the components of the composite primary endpoint. The results for the secondary endpoints are shown in Table 19 below and are discussed in more detail in the sections that follow.

Table 19: Secondary Endpoint Results for OCS Heart EXPAND Trial

Results for Secondary Endpoints (components of primary composite endpoint)	OCS (N=75)
Patient survival at day 30 post-transplantation	
Proportion (π[1]) (%) (n/N)[3]	94.6% (70/74)
95% CI (%) for Proportion[2]	(86.9%, 98.5%)
Incidence of severe PGD (left or right ventricle) in the first 24 hours post-transplantation	
Proportion (π[1]) (%) (n/N)	10.7% (8/75)
95% CI (%) for Proportion[2]	(4.7%, 19.9%)

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

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

[3] Excludes Subject (b)(6) who was retransplanted on Day 7.

6.1.18.1. Patient Survival at 30 Days Post-Transplant

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

6.1.18.2. Incidence of ISHLT Severe PGD (LV or RV) Post-transplantation

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

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

These results are comparable to, or in some cases, lower than the values reported in the literature. Table 20 below provides a detailed comparison of the studies citing PGD rates in the peer-reviewed literature. The earlier studies used various definitions of PGD, while more recent studies (2014 and later) used the ISHLT consensus definition that was used in the OCS Heart EXPAND trial. In addition, as noted in the table below, some of the studies presented limitations. For example, the study published by Sabatino, et al. (2017) was performed outside the U.S. and only 1% of subjects had VADs pre-transplant, which does not reflect the current U.S. heart transplant population nor the OCS Heart EXPAND trial's population with high VAD use. Two studies published from U.S. sites utilized the ISHLT criteria but noted that RV-PGD was not collected because the ISHLT criteria for RV-PGD rely upon pulmonary capillary wedge pressure, which is not routinely collected due to safety concerns. Despite these limitations, the literature provides a benchmark basis of comparison for the PGD results observed in the OCS Heart EXPAND trial.

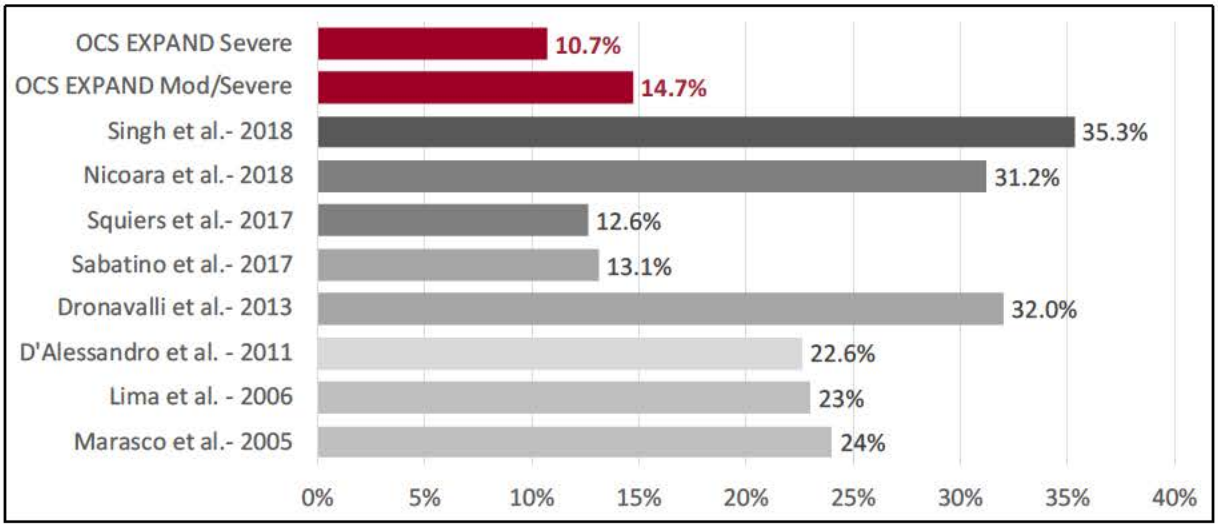
As shown in Figure 19 below, the results for OCS Heart EXPAND trial compare favorably to the results reported in the literature studies, even though the prior studies were primarily performed using standard criteria donor hearts, which present lower risk than the extended criteria donor hearts utilized in the OCS Heart EXPAND trial.

Table 20: Summary of Published Literature on PGD Following Heart Transplantation

Published Study	ISHLT criteria for PGD?	Reported incidence of PGD	Definition of PGD
Heart EXPAND 75 U.S. Recipients	Yes	10.7% (severe) 14.7% (moderate/severe)	ISHLT, moderate/severe Adjudicated by independent Medical Monitor
Dronavalli, et al., 2013 294 recipients in UK	No	32%	Severe impairment of systolic graft function affecting the right, left or both ventricles accompanied by hypotension, low cardiac output and high filling pressures in the absence of hyperacute rejection or technical factors
Marasco, et al., 2005 214 recipients in Australia	No	24%	Hypotension with a systolic blood pressure < 90 mmHg, low cardiac output (cardiac index < 2.0 liter/min/m^2) and pulmonary capillary wedge pressure > 20 mmHg after coming off cardiopulmonary bypass despite inotropic support
D'Alessandro, et al., 2011 402 recipients in France	No	23%	Need for extra-corporeal membrane oxygenation (ECMO) support in the immediate post-operative period
Lima, et al., 2006 260 recipients in the U.S.	No	23% (standard list) 26% (alternative list)	Requirement of high-dose inotrope use (epinephrine ≥ 0.07 µg/kg/min) and/or

Published Study	ISHLT criteria for PGD?	Reported incidence of PGD	Definition of PGD
Standard list, N=207, Alternative list, N=53			mechanical circulatory support immediately after transplantation
Nicoara, et al., 2018 317 recipients in U.S.	Yes	31.2%	ISHLT; moderate/severe
Singh, et al., 2018 450 recipients in UK	Yes	35.3%	ISHLT; moderate/severe
Squiers, et al., 2017 191 recipients in U.S.	Yes	12.6%	ISHLT; moderate/severe, LV-PGD only
Sabatino, et al., 2017 518 recipients in Italy; only 1% had VADs pre-transplant	Yes	13.1%	ISHLT; moderate/severe

Figure 19: Comparison of PGD Rates for OCS Heart EXPAND Trial and Published Literature



6.1.19. Primary Safety Endpoint

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

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

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

The incidence on moderate or severe PGD (LV or RV) was 14.7%, and one patient had primary graft failure requiring re-transplantation. The mean number of HGRSAEs per patient was 0.2 ± 0.37 (Table 21).

Table 21: Primary Safety Endpoint for OCS Heart EXPAND Trial and Listing of HGRSAEs by Type

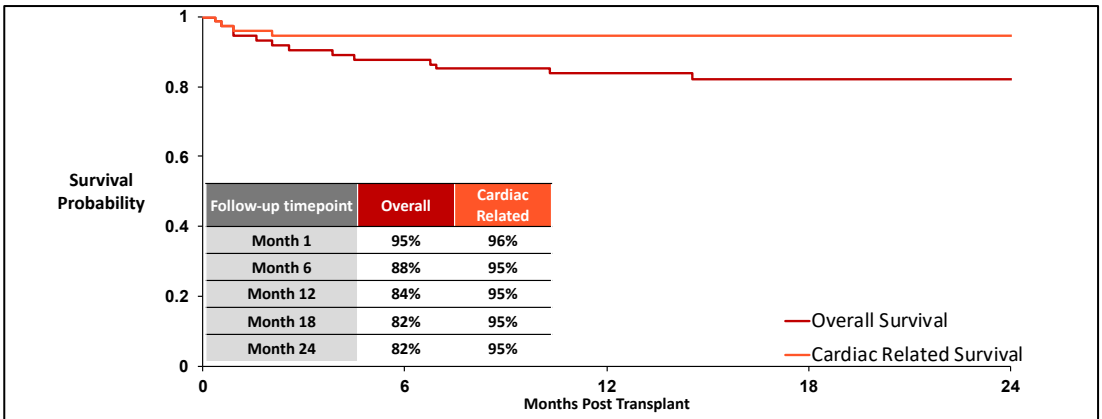
Primary Safety Endpoint and listing of HGRSAEs by type	OCS Heart EXPAND N = 75
Primary Safety Endpoint	
Mean ± SD	0.2 ± 0.37
Median	0.0
95% CI for Mean[1]	(0.1, 0.2)
HGRSAEs by Type	
Moderate or severe PGD (LV or RV), n/N (%)	11/75 (14.7%)
Primary Graft Failure requiring re-transplantation	1/75 (1.3%)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

NOTE: The FDA Panel Executive Summary states that all PGD discrepancies between the site investigators and the Medical Monitor (MM) involved the MM downgrading investigator determined severe PGD to be non-severe PGD. While this statement is factually correct, it should be noted that there were two cases of moderate PGD which were upgraded and added to the primary safety endpoint as a result of the MM adjudications, and another case cited in the FDA summary involved a patient whom the MM adjudicated as still meeting criteria for ISHLT severe PGD based on RV dysfunction. See Section 6.2.11 for further details.

6.1.20. Patient Survival

All transplanted recipients in the OCS Heart EXPAND trial have been followed through 12 months in the trial. In addition, survival data for the OCS Heart EXPAND subjects were obtained from the UNOS national database, giving follow-up beyond 12 months for subjects who had data entered in the database. The Kaplan-Meier Analysis of overall survival for OCS Heart EXPAND subjects is shown in Figure 20 below. Importantly, when considering the safety and effectiveness of the OCS Heart System as a heart preservation and assessment technology, it is clinically relevant to assess the number of cardiac-related deaths and to analyze cardiac related survival and not just overall survival, which could be confounded by other clinical variables in the complex nature of heart transplant recipients' medical course. There were 4 of a total of 13 deaths in the OCS Heart EXPAND trial through 14 months that were cardiac-related (Subjects (b)(6), (b)(6), (b)(6) and (b)(6)). Post-hoc Kaplan-Meier analysis of survival from cardiac-related death is also shown in Figure 20 below. Twelve-month freedom from cardiac-related death was 95% in the OCS Heart EXPAND trial.

Figure 20: Kaplan-Meier Analysis of Overall Survival and Cardiac-related Survival for OCS Heart EXPAND Subjects (N=75)



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

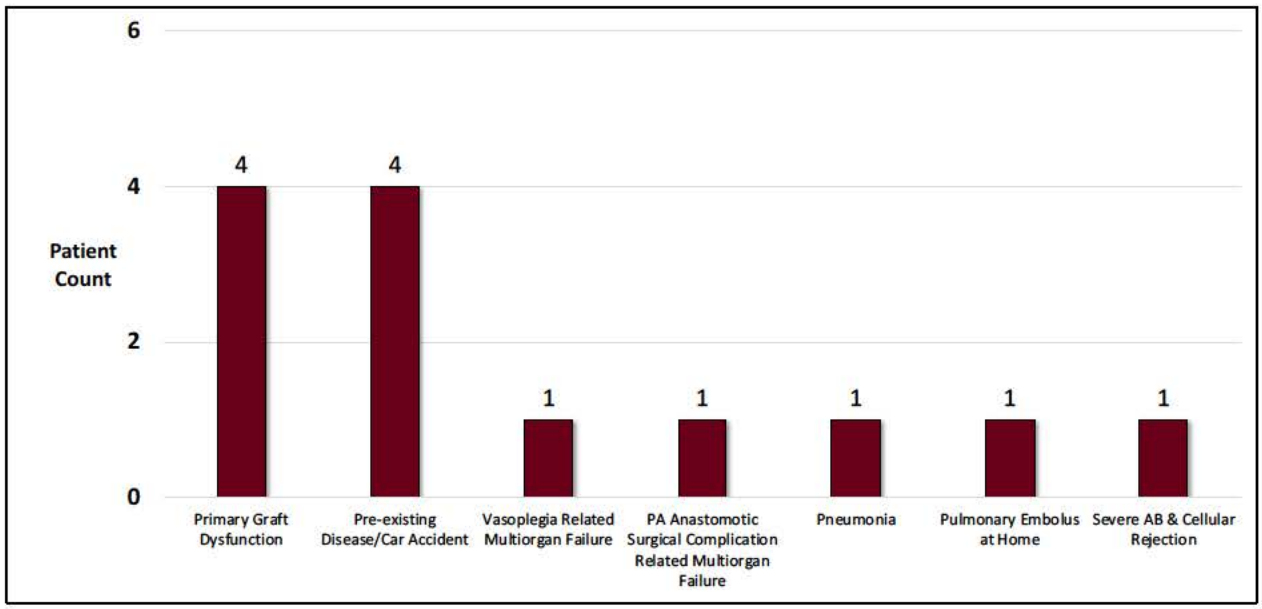
Timepoint	Month 0	Month 1	Month 6	Month 12	Month 18	Month 24
Overall	75	70	65	59	50	30
Cardiac Related	75	70	65	59	50	30

The causes of death for EXPAND subjects through 14 months post-transplant are illustrated in Figure 21 below. It is important to consider that 4 of 13 deaths in the OCS Heart EXPAND trial through 14 months (representing 5% of the overall mortality in the trial) were due to recipient factors and were not related to the transplanted heart, in general, or the use of the OCS Heart System:

- Subject (b)(6) died on Day 29 due to pre-existing chronic liver cirrhosis.
- Subject (b)(6) died on Day 80 and the subject likely had undiagnosed parenchymal lung disease leading to post-op acute respiratory distress disease.
- Subject (b)(6) died on Day 212 due to re-occurrence of pre-existing amyloidosis with refractory GI bleed.
- Subject (b)(6) died 14 months post-transplant due to motor vehicle accident that is unlikely to be related the transplant procedure or the transplanted heart.

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

Figure 21: Causes of Death in EXPAND Trial through 14 Months Post-transplant



Narratives for the patients who died in the OCS Heart EXPAND trial through 12 months post-transplant are provided in Appendix 3 of this document. The Medical Monitor adjudicated all deaths through 12 months post-transplant.

NOTE: FDA's Panel Executive Summary includes the results of statistical modelling to extrapolate EXPAND subject survival through 5 years post-transplant. This model was not shared with TransMedics during the review of this PMA.

TransMedics believes, based on statistical evidence developed by independent biostatisticians, that the models are highly questionable because they extrapolate EXPAND survival data through 5 years when approximately half of the data are censored prior to 2 years. In addition, TransMedics submitted evidence to demonstrate that the models have poor predictive validity and poor reliability (wide confidence intervals) and alternative models could be developed using other methods with widely varying results from the FDA models. Therefore, TransMedics believes that these models have statistical and scientific flaws and the discussion of the benefit-risk of the OCS Heart System should focus on the actual clinical data observed in the trial.

6.1.21. Serious Adverse Events (SAEs)

Table 22 below shows the adjudicated SAEs by System Organ Class for OCS Heart EXPAND subjects. All SAEs were reviewed and adjudicated by the Medical Monitor. The Cardiac disorders System Organ Class includes 16 patients who experienced SAEs related to electrical or rhythm disorders, which are commonly experienced by heart transplant recipients.

Table 22: List of Adjudicated SAEs By System Organ Class and Preferred Term – Transplanted Recipient Population through 30 Days of Follow-up

System Organ Class	Preferred Term	Subjects N=75	Events
Total		56 (74.7%)	106 (100%)
Cardiac disorders		31 (41.3%)	38 (35.8%)
	Arrhythmia	4 (5.3%)	4 (3.8%)
	Arrhythmia supraventricular	1 (1.3%)	1 (0.9%)
	Atrial fibrillation	5 (6.7%)	5 (4.7%)
	Atrial flutter	1 (1.3%)	1 (0.9%)
	Atrial tachycardia	1 (1.3%)	1 (0.9%)
	Atrioventricular block	1 (1.3%)	1 (0.9%)
	Bradycardia	1 (1.3%)	1 (0.9%)
	Cardiac failure congestive	4 (5.3%)	4 (3.8%)
	Cor pulmonale	2 (2.7%)	2 (1.9%)
	Electromechanical dissociation	1 (1.3%)	1 (0.9%)
	Left ventricular dysfunction	5 (6.7%)	4 (4.7%)
	Left ventricular failure	1 (1.3%)	1 (0.9%)
	Nodal rhythm	1 (1.3%)	1 (0.9%)
	Pericardial effusion	5 (6.7%)	5 (4.7%)
	Right ventricular dysfunction	4 (5.3%)	4 (3.8%)
	Right ventricular failure	1 (1.3%)	1 (0.9%)
Congenital, familial and genetic disorders		1 (1.3%)	1 (0.9%)
	Atrial septal defect	1 (1.3%)	1 (0.9%)
General disorders and administration site conditions		1 (1.3%)	1 (0.9%)
	Multi-organ failure	1 (1.3%)	1 (0.9%)
Hepatobiliary disorders		1 (1.3%)	1 (0.9%)
	Hepatic failure	1 (1.3%)	1 (0.9%)
Immune system disorders		12 (16.0%)	12 (11.3%)
	Heart transplant rejection	12 (16.0%)	12(11.3%)
Infections and infestations		4 (5.3%)	4 (3.8%)

System Organ Class	Preferred Term	Subjects N=75	Events
	Clostridial infection	1 (1.3%)	1 (0.9%)
	H1N1 influenza	1 (1.3%)	1 (0.9%)
	Pneumonia	1 (1.3%)	1 (0.9%)
	Sepsis	1 (1.3%)	1 (0.9%)
Injury, poisoning and procedural complications		9 (12.0%)	10 (9.4%)
	Cardiac procedure complication	3 (4.0%)	3 (2.8%)
	Heart injury	1 (1.3%)	1 (0.9%)
	Operative haemorrhage	1 (1.3%)	1 (0.9%)
	Post-operative thoracic procedure complication	1 (1.3%)	1 (0.9%)
	Procedural complication	2 (2.7%)	2 (1.9%)
	Rectal laceration post-operative	1 (1.3%)	1 (0.9%)
	Vascular pseudoaneurysm	1 (1.3%)	1 (0.9%)
Metabolism and nutrition disorders		1 (1.3%)	1 (0.9%)
	Fluid overload	1 (1.3%)	1 (0.9%)
Nervous system disorders		6 (8.0%)	6 (5.7%)
	Cerebrovascular accident	3 (4.0%)	3 (2.8%)
	Convulsion	2 (2.7%)	2 (1.9%)
	Vocal cord paralysis	1 (1.3%)	1 (0.9%)
Psychiatric disorders		3 (4.0%)	3 (2.8%)
	Delirium	3 (4.0%)	3 (2.8%)
Renal and urinary disorders		12 (16.0%)	12 (11.3%)
	Renal failure acute	10 (13.3%)	10 (9.4%)
	Renal impairment	2 (2.7%)	2 (1.9%)
Respiratory, thoracic and mediastinal disorders		14 (18.7%)	15 (14.2%)
	Acute respiratory distress syndrome	1 (1.3%)	1 (0.9%)
	Acute respiratory failure	2 (2.7%)	2 (1.9%)
	Hydrothorax	1 (1.3%)	1 (0.9%)
	Hypoxia	1 (1.3%)	1 (0.9%)

System Organ Class	Preferred Term	Subjects N=75	Events
	Pleural effusion	3 (4.0%)	3 (2.8%)
	Respiratory distress	1 (1.3%)	1 (0.9%)
	Respiratory failure	6 (8.0%)	6 (5.7%)
Vascular disorders		2 (2.7%)	2 (1.9%)
	Hemorrhage	1 (1.3%)	1 (0.9%)
	Subclavian vein thrombosis	1 (1.3%)	1 (0.9%)

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

6.1.22. Analysis of Donor Hearts Turned Down following OCS Preservation

Of the 93 donor hearts instrumented on OCS, 18 donor hearts (matched to 16 subjects) did not meet transplantability criteria following preservation on OCS Heart System and were not transplanted, and 75 of 93 donor hearts were successfully transplanted after OCS Heart System preservation and assessment (81% utilization rate as defined in the protocol). The mean UNOS donor match run refusals for the turned down hearts was 80.7, indicating that they most likely would not have been utilized outside of the Heart EXPAND trial. These turned down donor hearts exhibited unstable and rising lactate trends despite multiple attempts by the user to optimize perfusion parameters. Figure 22 below illustrates the mean lactate values for all 18 hearts that were turned down after OCS Heart System assessment as compared to the OCS Heart System lactate profile for the donor hearts that were transplanted in the OCS Heart EXPAND trial.

The disposition of the 16 recipients that were initially matched to these 18 turned down hearts were as follows:

- 12 patients were transplanted outside of the study with a second donor heart offer that was standard criteria and was preserved on cold storage.
- 1 patient was transplanted in the OCS Heart EXPAND trial with another donor heart preserved with OCS Heart System.
- 3 patients remained on the waiting list awaiting another donor heart offer at the conclusion of the study. One of these 3 patients died on the waiting list while waiting for another donor heart offer, and 2 patients were alive on the waiting list at the conclusion of the study.

The clinical case summary for each of these turned down organs and the status of the intended recipients is provided in Table 23 below. Analysis of the pathology of the turned down donor hearts was performed by an independent core pathologist, and a summary of the pathology findings are also included in Table 23.

FDA's Panel Executive Summary asserts that, based on FDA's interpretation of pathology reports, that OCS Heart System may have caused damage to the donor hearts during perfusion that may have caused these hearts to be turned down for transplantation. TransMedics respectfully refutes this assertion based on the following objective clinical facts:

- Brain death is associated with significant physiologic changes that could show as pathological findings of a donor heart on histological examination of the myocardium;
- The donor hearts studied in the OCS Heart EXPAND trial were hearts with significant risk factors that made them highly unlikely to be used for transplantation. Many of these risk factors could contribute to pathological findings in histological examination of the myocardium;
- The FDA analysis disregards the potential of these hearts being inherently damaged by the insult of brain death and associated risk factors described above;
- Many of the subjective findings cited by FDA such as "myocardial petechiae" are commonly seen in routine cardiac bypass open heart surgeries and with no major clinical negative impact on heart function; and
- To our knowledge, there has never been any published or presented reports of any clinical or pre-clinical data directly or indirectly linking OCS Heart System to myocardial injury during perfusion.

NOTE: FDA's Panel Executive Summary asserts that based on FDA's interpretation of pathology reports, that OCS Heart System may have caused damage to the donor hearts during perfusion that may have caused these hearts to be turned down for transplantation. TransMedics respectfully refutes these observations based on the clinical facts outlined above and based on the analyses and interpretation of the independent expert core pathologist.

Figure 22: Mean Arterial Lactate Trend on the OCS Heart System for All Turned Down Donor Hearts Compared to Hearts that were Transplanted in the OCS Heart EXPAND Trial

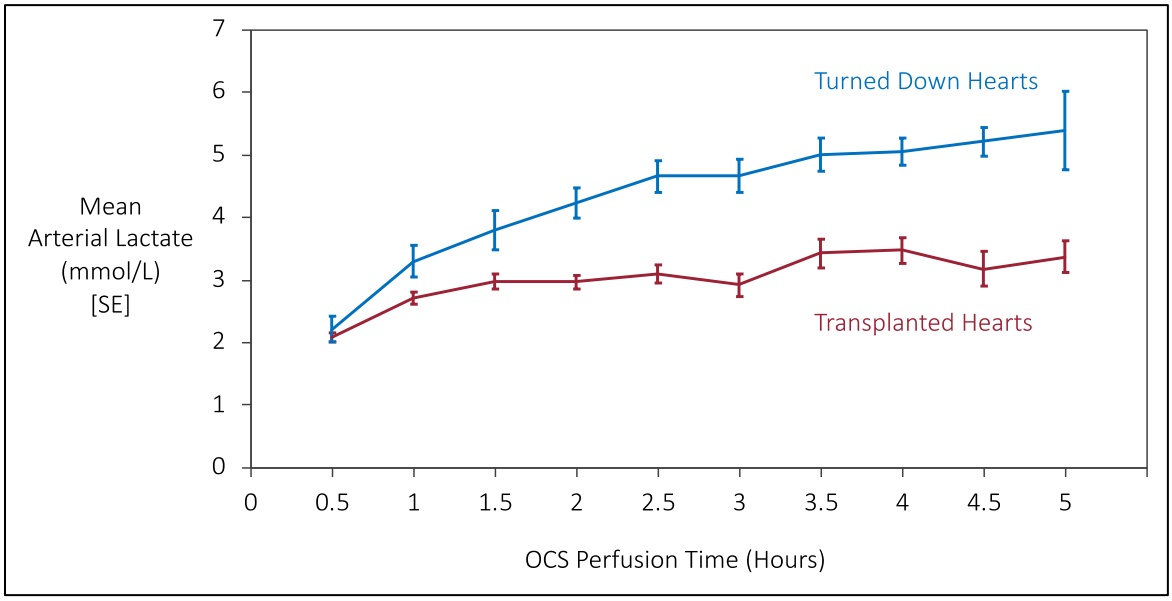


Table 23: Case Summaries for Donor Hearts that Failed to Meet Transplantability Criteria in the OCS Heart EXPAND Trial

Subject ID	Donor Eligibility Characteristics	Pathology Findings	Clinical Reason for Failure to Meet Transplantability Criteria	Recipient Disposition
(b)(6)	Expected cross-clamp time ≥ 4 hrs Downtime ≥ 20 mins	Papillary muscle and anterior left ventricle showed a healing infarct correlating with the arrest and downtime approximately 3.5 days prior to donor heart retrieval.	Organ was declined due to inability to wean off pacing or regain native sinus rhythm; continuous rising (and often secreting) lactate despite attempts to optimize mean AOP and CF.	Subject returned to the transplant waiting list and was transplanted outside of the trial with a different organ that did not meet OCS Heart EXPAND donor criteria preserved on cold storage.
(b)(6)	Expected cross-clamp time ≥ 4 hrs.	Mild biventricular hypertrophy with focal endocardial and myocardial hemorrhage.	Organ was declined due to continuous rising (and often secreting) lactate despite attempts to optimize mean AOP and CF.	Subject returned to the transplant waiting list and was matched with another OCS Heart EXPAND donor heart (described below).
(b)(6)	Expected cross-clamp time ≥ 4 hrs.	Evidence of ischemic injury involving primarily the subendocardial aspect of the mid-portion of the anterior-lateral left ventricle. Insult appears to precede normothermic sanguineous circulation by at least 12-18 hrs but less than 48 hrs.	Organ was declined due to continuous rising (and often secreting) lactate despite attempts to optimize mean AOP and CF.	Subject returned to the transplant waiting list and was transplanted outside of the trial with a different organ that did not meet OCS Heart EXPAND donor criteria preserved on cold storage.
(b)(6)	Downtime ≥ 20 min; LVH	Evidence of recent ischemic injury involving primarily the subendocardial aspect of the posterior and lateral left ventricle and interventricular septum. Insult appears to precede normothermic sanguineous circulation by 24 hrs but less than 36 hrs.	Organ was declined due to continuous rising (and often secreting) lactate despite attempts to optimize mean AOP and CF.	Subject returned to the transplant waiting list and was still on the waiting list at time of enrollment completion.
(b)(6)	Downtime ≥ 20 min; Luminal irregularities	LV posterior wall thickness 14mm-unknown at time of procurement. Recent and extensive ischemic injury involving primarily the subendocardial aspect of the mid-portion of the anterior-lateral left ventricle. Insult appears to precede normothermic sanguineous circulation by at least 12-18 hrs but less than 48 hrs.	Organ was declined due to continuous rising lactate despite attempts to optimize mean AOP and CF.	Subject returned to the transplant waiting list and subsequently died on the waiting list while waiting for another donor offer.
(b)(6)	Expected cross-clamp time ≥ 4 hrs Downtime ≥ 20 min	Evidence of extensive ischemic injury involving both left and right ventricles and interventricular septum. Insult appears to precede normothermic sanguineous circulation by 24 hrs but less than 36 hrs.	Organ was declined due to continuous rising lactate despite attempts to optimize mean AOP and CF.	Subject returned to the transplant waiting list and was transplanted outside of the trial with a different organ that did not meet OCS Heart EXPAND donor criteria preserved on cold storage.

Subject ID	Donor Eligibility Characteristics	Pathology Findings	Clinical Reason for Failure to Meet Transplantability Criteria	Recipient Disposition
(b)(6)	Expected cross-clamp time ≥ 4 hrs	Mild coronary artery atherosclerosis with ~10% luminal narrowing. Widespread patchy ischemic-type cardiac myocyte injury primarily involving the anterior and superior left ventricle. Areas of myofiber hyper-eosinophilia, interstitial edema, contraction band necrosis, and wavy myofibers are seen. The ischemic insult occurred between 12-18hr before tissue fixation and subsequent sampling.	Organ was declined due to continuous rising lactate despite attempts to optimize mean AOP and CF.	Subject returned to the transplant waiting list and was still on the waiting list at the end of trial enrollment.
(b)(6)	Expected cross-clamp time ≥ 4 hrs; Downtime ≥ 20 min	Mild atherosclerotic coronary artery disease. Evidence of recent ischemic injury involving primarily the subendocardial aspect of the mid-portion of the anterior-lateral left ventricle. The insult appears relatively recent: > 8-12 hours and probably < 36 hrs of time subjected to normothermic sanguineous circulation.	Organ was declined due to continuous rising lactate despite attempts to optimize mean AOP and CF.	Subject returned to the transplant waiting list and was subsequently transplanted on-study with another organ preserved on OCS.
(b)(6)	Luminal irregularities	Mild coronary artery atherosclerosis with < 20% luminal narrowing. Widespread patchy left ventricular ischemic injury, focally severe with an infarct involving subendocardial anterior left ventricle.	Organ was declined due to continuous rising (and often secreting) lactate despite attempts to optimize mean AOP and CF; final arterial lactate ≥ 5 mmol/L.	Subject returned to the transplant waiting list and was transplanted outside of the trial with a different organ that did not meet OCS Heart EXPAND donor criteria preserved on cold storage.
(b)(6)	Downtime ≥ 20min; Diabetes	Focally moderate coronary artery fibro-intimal hyperplasia with atherosclerotic plaque resulting in ~40% luminal narrowing. Patchy ischemic injury manifests as interstitial edema and contraction band necrosis from the anterior left ventricle and left ventricular papillary muscles.	Organ was declined due to continuous rising (and often secreting) lactate despite attempts to optimize mean AOP and CF; final arterial lactate ≥ 5 mmol/L.	Subject returned to the transplant waiting list and was matched with another OCS Heart EXPAND donor (described below).
(b)(6)	LVEF 40% -50%; Alcoholism	Mild coronary artery atherosclerosis with 15% luminal narrowing. Widespread patchy left ventricular ischemic injury, focally severe in the left lateral ventricle and papillary muscles and present in sections of the posterior-superior left ventricle and septum. Ischemic insult estimated as occurring > 12 hrs prior	Organ was declined due to continuous rising (and often secreting) lactate despite attempts to optimize mean AOP and CF; final arterial lactate ≥ 5 mmol/L.	Subject returned to the transplant waiting list and was transplanted outside of the trial with a different organ that did not meet OCS Heart EXPAND donor criteria preserved on cold storage.

Subject ID	Donor Eligibility Characteristics	Pathology Findings	Clinical Reason for Failure to Meet Transplantability Criteria	Recipient Disposition
		to normothermic sanguineous circulation.		
(b)(6)	Donor age 45-55 years old, with no coronary catheterization data.	Mild coronary artery atherosclerosis with ~20% luminal narrowing. Focally calcified coronary artery atherosclerosis of the left anterior descending coronary artery. Focal ischemic-type cardiac myocyte injury primarily involving the left and left posterior and left anterior ventricular apex. The insult likely occurred between 12 and 24 hrs before histopathological sampling.	Organ was declined due to continuous rising (and often secreting) lactate despite attempts to optimize mean AOP and CF; final arterial lactate ≥ 5 mmol/L.	Subject returned to the transplant waiting list and was transplanted outside of the trial with a different organ that did not meet OCS Heart EXPAND donor criteria preserved on cold storage.
(b)(6)	Expected cross-clamp time ≥ 4 hrs; Downtime ≥ 20 min	Extensive ischemic injury involving the entire circumference of the left ventricle, worse in the interventricular septum. Insult preceded normothermic sanguineous circulation > 24 hrs.	Organ was declined due to continuous rising (and often secreting) lactate despite attempts to optimize mean AOP and CF; final arterial lactate ≥ 5 mmol/L, right heart failure.	Subject returned to the transplant waiting list and was transplanted outside of the trial with a different organ that did not meet OCS Heart EXPAND donor criteria preserved on cold storage.
(b)(6)	Downtime ≥ 20 min; Donor age > 55 yrs; Luminal irregularities	Evidence of ischemic injury involving primarily the left and right ventricle and worse subendocardial regions of the left ventricle. Insult appears to precede normothermic sanguineous circulation > 24 hrs.	Organ was declined due to continuous rising (and often secreting) lactate despite attempts to optimize mean AOP and CF; final arterial lactate ≥ 5 mmol/L.	Subject returned to the transplant waiting list and was transplanted outside of the trial with a different organ that did not meet OCS Heart EXPAND donor criteria preserved on cold storage.
(b)(6)	LVEF 40-50%; Downtime ≥ 20 min	Evidence of extensive ischemic injury involving primarily the left ventricle, worse in the anterior and posterior left ventricle. Insult appears to precede normothermic sanguineous circulation > 24 hrs.	Organ was declined due to continuous rising (and often secreting) lactate despite attempts to optimize mean AOP and CF; RV Failure.	Subject returned to the transplant waiting list and was transplanted outside of the trial with a different organ that did not meet OCS Heart EXPAND criteria preserved on cold storage.
(b)(6)	Expected cross-clamp time ≥ 4 hrs; Luminal irregularities	Mild coronary artery atherosclerosis with ~25% luminal narrowing. Widespread ischemic-type injury primarily involving the left and right ventricles and interventricular septum. The insult likely occurred > 36 hrs before histopathological sampling.	Organ was declined due to continuous rising (and often secreting) lactate despite attempts to optimize mean AOP and CF.	Subject returned to the transplant waiting list and was transplanted outside of the trial with a different organ that did not meet OCS Heart EXPAND donor criteria preserved on cold storage.
(b)(6)	Expected cross-clamp time ≥ 4 hrs; Downtime ≥ 20 min	No pathology available. Medical Examiner from donor region ordered the tissue be returned for medico-legal post-mortem examination.	Organ was declined due to continuous rising (and often secreting) lactate despite attempts to optimize mean	Subject returned to the transplant waiting list and was transplanted outside of the trial with a different organ that did not meet OCS

Subject ID	Donor Eligibility Characteristics	Pathology Findings	Clinical Reason for Failure to Meet Transplantability Criteria	Recipient Disposition
			AOP and CF; final arterial lactate ≥ 5 mmol/L.	Heart EXPAND donor criteria preserved on cold storage.
(b)(6)	LVEF 40-50%	Widespread patchy ischemic-type cardiac myocyte injury primarily involving the left posterior ventricle near the apex; focally seen in the right and left ventricles and inter-ventricular septum. The insult likely occurred > 24 - 48 hrs before histopathological sampling	Organ was declined due to continuous rising (and often secreting) lactate despite attempts to optimize mean AOP and CF; final arterial lactate ≥ 5 mmol/L.	Subject returned to the transplant waiting list and was transplanted outside of the trial with a different organ that did not meet OCS Heart EXPAND donor criteria preserved on cold storage.

6.1.23. Conclusions of the OCS Heart EXPAND Trial

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

- An analysis of risk factors for donor hearts from the national UNOS/SRTR registry data demonstrated that the OCS Heart EXPAND trial enrolled donor hearts that are seldom or rarely transplanted in the U.S. today using ischemic cold storage. The use of the OCS Heart System resulted in successful transplantation of 81% of these types of donor hearts. This finding supports the benefit of the OCS Heart System to expand the donor pool to increase the number of heart transplants performed in the U.S.
- The OCS Heart EXPAND trial met its primary effectiveness composite endpoint of 30-day patient survival and freedom from severe ISHLT PGD with an 88% success rate on the primary effectiveness composite endpoint ($p<0.0001$).
- The 30-day patient survival in the OCS Heart EXPAND trial of 94.6% is comparable to contemporary standard criteria heart transplant survival in the U.S. (Colvin, et al., 2020).
- The incidence of severe ISHLT PGD post-transplant of 10.7% in the OCS Heart EXPAND trial is comparable to or lower than contemporary rates of severe heart PGD published in the literature.
- The OCS Heart EXPAND trial long-term patient survival at 6 and 12 months post-transplant was 88% and 84%, respectively. Post-hoc analysis of cardiac graft-related survival was 95% at 6 months and 12 months post-transplant, respectively.
- The OCS Heart EXPAND trial demonstrated the safety of the OCS Heart System. The mean number of HGRSAEs per patient was 0.2 ± 0.37 with an overall safety profile that was consistent with routine heart transplantation.
- Serious Adverse Events were typical for patients undergoing heart transplantation, and do not raise any signals for concern.

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

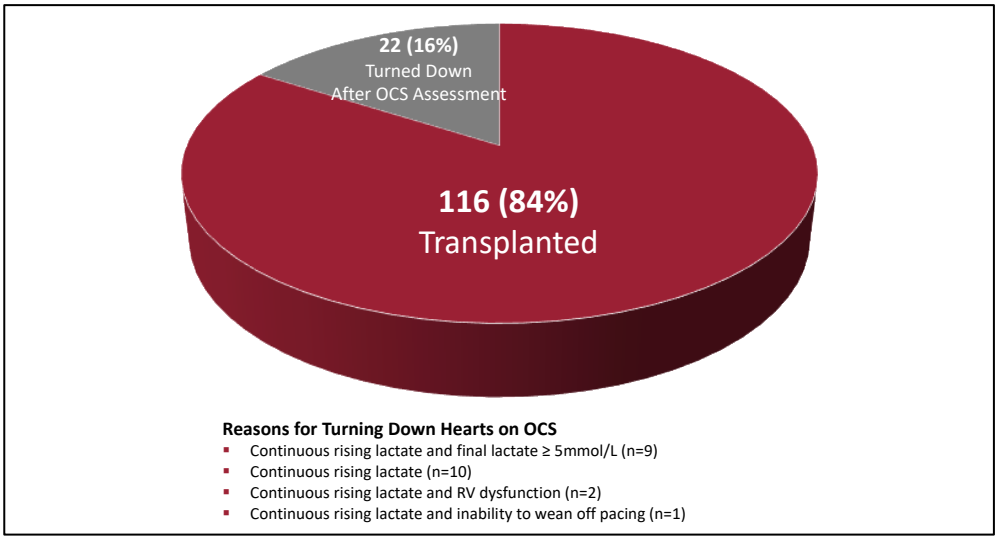
FDA approved a CAP for the OCS Heart EXPAND trial for an additional 75 patients. As of the date of database closure, in the OCS Heart EXPAND CAP, 49 donor hearts had been perfused on OCS, 45 patients have been transplanted and 41 of 45 of these transplanted recipients had a minimum of 30 days follow-up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

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

6.2.1. Donor Heart Utilization

As of the date of database closure, 138 donor hearts were perfused and assessed on the OCS Heart System in the combined OCS Heart EXPAND + CAP population. The utilization rate, as defined in the protocol, was 84.0%, with 116 of 138 extended criteria donor hearts successfully transplanted (Figure 23).

Figure 23: Donor Heart Utilization in OCS Heart EXPAND Trial and OCS Heart EXPAND CAP Pooled Analysis



This is a clinically important result, given that donor hearts were rejected by other centers and likely would not have been utilized outside of the OCS Heart EXPAND trial and OCS Heart EXPAND CAP. Table 24 below shows the donor match run data available from UNOS/SRTR for the combined OCS Heart EXPAND + CAP donor hearts which shows that these donor hearts were refused by other centers a mean of 59.7 times.

Table 24: UNOS Donor Match Run Donor Heart Offers Refusals Prior to Acceptance in OCS Heart EXPAND Trial and OCS Heart EXPAND CAP

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

6.2.2. Transplanted Recipient Population

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

6.2.3. Recipients Demographic Characteristics and Risk Factors

The recipient demographics are shown in Table 25 below. The majority of recipients (64%) were UNOS Urgency Status IA and were on mechanical circulatory support at the time of transplant (75%, 87/116).

Table 25: Summary of Recipient Characteristics for Combined OCS Heart EXPAND + CAP

Recipient Characteristics	OCS Transplanted Recipients N=116
Age (years) mean ± SD	54.3 ± 13.2
Age > 65 years	25/116 (21.6%)
Gender – male n (%)	93 (80.2%)
BMI (kg/m^2) – mean ± SD	28.3 ± 4.7
Race	
• Asian	2 (1.7%)
• Black or African American	24 (20.7%)
• Native Hawaiian or Other Pacific Islander	1 (0.9%)
• White	86 (74.1%)
• Other	2 (1.7%)
• Not Provided	1 (0.9%)
History of Mechanical Circulatory Support	87 (75.0%)
• LVAD	58 (50.0%)

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

6.2.4. Donor Characteristics and Risk Factors

Donor inclusion criteria/risk factors are provided in Table 26 below. Among these 116 transplanted recipients, 52 (44.8%) received donor hearts that met multiple donor inclusion criteria.

Table 26: Donor Inclusion Criteria Met for Transplanted Donor Hearts for OCS Heart EXPAND + CAP

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

Donor Inclusion Criteria Met n (%)*	OCS Transplanted Donors N=116
LVH	22/116 (19.0%)
Downtime ≥ 20 min	33/116 (28.4%)
LVEF 40% -50%	27/116 (23.3%)
Luminal irregularities	10/116 (8.6%)
Alcoholism	16/116 (13.8%)
Carbon Monoxide as cause of death	1/116 (0.9%)
Diabetes	3/116 (2.6%)
Donor Age 45-55 with no coronary cath data	1/116 (0.9%)
Donors with Multiple Criteria	52/116 (44.8%)
* Donor inclusion criteria presented reflect additional review and verification of source documentation by TransMedics during PMA review.	

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

FDA's Panel Executive Summary has questioned whether the donor hearts in the OCS Heart EXPAND and CAP trials are "extended criteria" and has asserted that the donor hearts in the OCS Heart EXPAND and CAP trials are "generally clinically similar to the donors in PROCEED II." Similar to the analysis described in Section 6.1.13 for the OCS Heart EXPAND trial, we performed an analysis of donor data from the national UNOS/SRTR database of standard criteria donors transplanted today using cold storage compared to the combined OCS Heart EXPAND + CAP population.

For this analysis, the N=138 donor hearts in the OCS Heart EXPAND + CAP population are compared to 10,873 donor hearts transplanted over the time period of January 2015-March 2019, which excludes any recipients of OCS donor hearts. Similar to the analysis in Section 6.1.13, this analysis demonstrates that the donor hearts included in the OCS Heart EXPAND and OCS Heart EXPAND CAP are not routinely transplanted today (Table 27).

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

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

The data demonstrate that the EXPAND + CAP donors are not routinely transplanted on cold storage in the U.S. today. This is further demonstrated when considering donors transplanted in the U.S. on cold storage with two or more criteria (which comprised 45% of donor hearts in the EXPAND + CAP population). As shown in Table 27 below, of the 10,873 donor hearts preserved on cold storage:

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

Table 27: Donor Characteristics for EXPAND + CAP Heart Population vs. UNOS/SRTR Hearts Transplanted 2015- March 2019

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

These data, in conjunction with the UNOS donor match run described in Table 24 above, show that the donor hearts transplanted in the combined OCS Heart EXPAND + CAP population are not routinely transplanted in the U.S. today on cold storage and this is an important clinical

consideration in the assessment of the benefits and risks of the OCS Heart System to increase the number of successful heart transplants in the U.S.

6.2.6. Donor Demographics

Donor demographics for the N=138 transplanted donor hearts are shown in Table 28 below.

Table 28: Donor Characteristics for Transplanted Donors in OCS Heart EXPAND CAP by Donor Inclusion Criteria Met (N=116)

	Diabetes + negative for CAD N=3	Alcoholism w/good cardiac function N=16	Age ≥ 55 N=12	Luminal irregularities N=10	LVEF ≥ 40% and ≤ 50% N=27	Downtime ≥ 20 mins N=33	LVH N=22	Expected Cross-clamp Time ≥ 4 hours N=53	ALL Donors N=116
Cross-clamp Time (min) Mean ± SD	301.7 ± 17.2	376.3 ± 83.0	347.8 ± 52.6	365.1 ± 127.2	355.0 ± 84.6	357.5 ± 80.4	355.3 ± 83.8	423.0 ± 88.7	381.3 ± 91.0
Donor Age (yr) Mean ± SD	50.9 ± 9.4	44.4 ± 10.3	56.0 ± 0.9	45.6 ± 9.2	32.3 ± 10.0	34.0 ± 9.9	41.8 ± 11.6	35.3 ± 11.7	37.1 ± 11.8
LV Septal wall thickness (mm) N Mean ± SD	3 10.67 ± 1.16	16 10.03 ± 1.84	12 10.50 ± 2.02	9 11.88 ± 1.97	24 10.27 ± 2.16	30 10.23 ± 2.34	22 12.68 ± 1.73	43 9.38 ± 1.63	102 10.09 ± 2.16
Reported Downtime (mins) N Mean ± SD	--	6 11.7 ± 7.2	2 31.0 ± 41.0	6 28.5 ± 20.9	12 31.3 ± 31.5	28 41.1 ± 27.4	14 31.1 ± 29.5	14 25.6 ± 33.4	47 28.6 ± 26.2
LVEF (%) N Mean ± SD	3 56.7 ± 14.43	16 62.8 ± 7.45	12 62.8 ± 7.12	10 59.2 ± 5.45	27 46.7 ± 3.52	33 57.9 ± 7.40	22 59.3 ± 7.72	52 61.1 ± 7.25	115 58.2 ± 8.44
Additional Donor Characteristics									
Male Sex N (%)									89 (66.7%)
BMI (kg/m^2)									27.8 ± 6.7

6.2.7. Donor Heart Preservation Characteristics and Critical Times

OCS perfusion time, total ischemic time and cross-clamp time are listed in Table 29 below for the 116 transplanted recipients in the combined analysis.

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

Table 29: Preservation Characteristics for Donor Hearts for Combined OCS Heart EXPAND CAP and OCS Heart EXPAND Trial Cohort (N=116)

Parameter	OCS (N=116)
Cross-clamp Time (mins)[1]	116
Mean ± SD	381.3 ± 90.98
Median	375.0
Min.- Max.	173 - 682
Total Ischemic Time (mins)[2]	116
Mean ± SD	102.8 ± 22.41
Median	98.0
Min.- Max.	65 - 189
OCS Perfusion Time (mins)	116
Mean ± SD	278.5 ± 80.84
Median	278.0
Min.- Max.	100 - 532

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

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

6.2.8. OCS Heart System Perfusion Parameters

The OCS perfusion parameters are summarized in Table 30 below for both transplanted and turned down donor hearts.

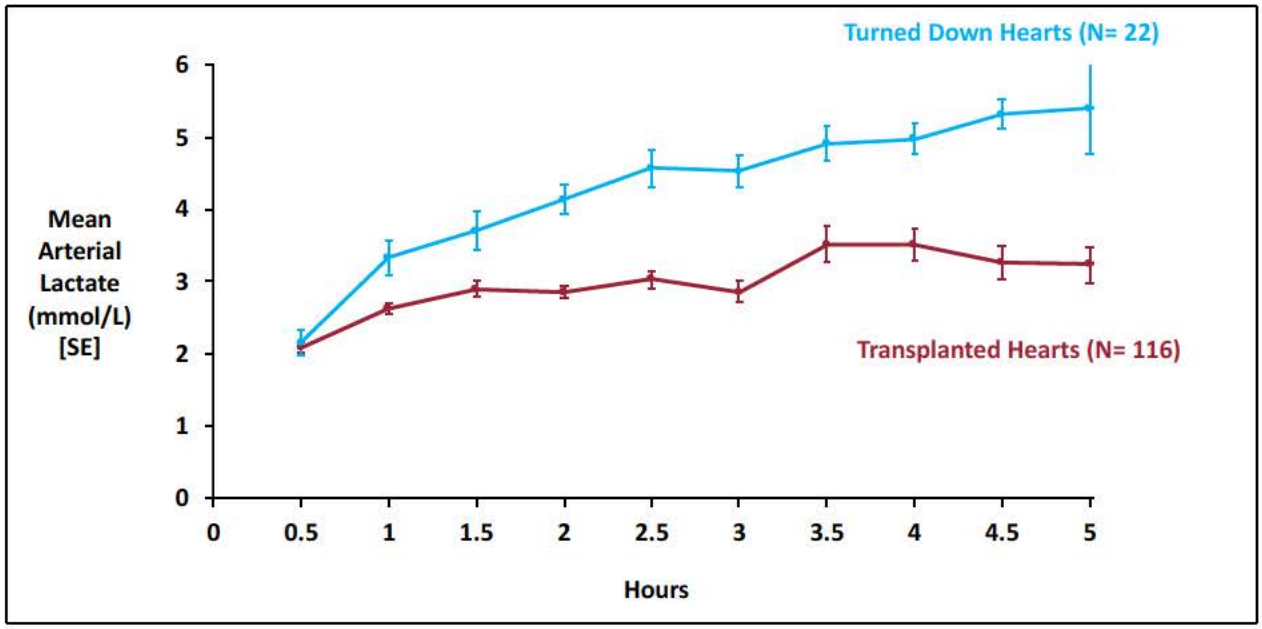
Table 30: OCS Heart System Perfusion Parameters for Donor Hearts for Combined OCS Heart EXPAND Trial and OCS Heart EXPAND CAP

Parameter	OCS (N=116)	Turn Down (N=22)
Pump Flow Mean (L/min)		
N	116	22
Mean ± SD	1.119 ± 0.1141	1.143 ± 0.1110
Median	1.110	1.106
Minimum - Maximum	0.89 - 1.76	1.01 - 1.44
Coronary Flow Mean (L/min)		
N	116	22
Mean ± SD	0.749 ± 0.1284	0.744 ± 0.1650
Median	0.777	0.788
Minimum - Maximum	0.06 - 0.99	0.15 - 0.92
AOP Mean (mmHg)		
N	116	22
Mean ± SD	79.9 ± 8.23	82.1 ± 8.26
Median	80.9	83.4
Minimum - Maximum	48 - 102	59 - 97
Initial Arterial Lactate (mmol/L)		
N	116	22
Mean ± SD	1.894 ± 0.7165	2.239 ± 0.9053
Median	1.735	2.000
Minimum - Maximum	0.67 - 5.70	1.06 - 4.47
Final Arterial Lactate (mmol/L)		
N	116	22
Mean ± SD	3.017 ± 1.0679	5.193 ± 1.0363
Median	2.835	4.885
Minimum - Maximum	0.55 - 7.59	3.50 - 7.89

Figure 24 below displays the average lactate trend for all donor hearts on the OCS Heart System that were accepted for transplantation in the OCS Heart EXPAND + CAP population compared to those that were turned down for transplantation. There was a substantial difference between the overall lactate trend of hearts that were transplanted vs. the hearts that were turned down after OCS Heart assessment.

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

Figure 24: Mean Arterial Lactate Over Time in OCS Heart EXPAND +CAP Combined Transplanted Donor Hearts (N=116) vs. Turned Down Hearts (N=22)



6.2.9. Primary and Secondary Endpoint Results

Table 31 below shows the results of the composite primary effectiveness endpoint for the combined OCS Heart EXPAND + CAP population. The primary effectiveness endpoint met the pre-specified objective performance goal of 65% with 91% of the subjects achieving success on the composite endpoint of patient survival at Day 30 post-transplantation and absence of severe ISHLT PGD in the first 24 hours post-transplantation.

The secondary endpoints are shown in Table 32. The 30-day survival of 96.5% in the combined OCS Heart EXPAND + CAP population is comparable to contemporary standard criteria heart transplant survival in the U.S (96%; Colvin, et al., 2020). The incidence of severe ISHLT PGD of 7.8% is lower than contemporary rates of severe heart PGD published in the literature.

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

Table 31: Primary Effectiveness Endpoint for the Combined OCS Heart EXPAND + CAP Population

Results for Primary Endpoint Composite	OCS (N=116)
Patient survival at day 30 post-transplantation and absence of severe PGD (left or right ventricle) in the first 24 hours post-transplantation	
Proportion (π^1) (%) (n/N)	106/116 (91.4%)
95% CI (%) for Proportion[2]	(0.847, 0.958)

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

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

Table 32: Secondary Endpoint Results for the Combined OCS Heart EXPAND + CAP Population

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

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

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

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

6.2.10. Donor Heart Utilization

In the combined OCS Heart EXPAND + CAP population, 116 of 138 donor hearts preserved on OCS were successfully transplanted (84% utilization rate as defined in the protocol). The turned down donor hearts exhibited unstable and rising lactate trends despite multiple attempts by the user to optimize perfusion parameters. Figure 24 above illustrates the mean lactate values for the 22 hearts that were turned down after OCS Heart System assessment in the combined OCS Heart EXPAND + CAP population as compared to the OCS Heart System lactate profile for the donor hearts that were transplanted.

6.2.11. Primary Safety Endpoint

The primary safety endpoint for the combined OCS Heart EXPAND + CAP population was 0.2 ± 0.37 (Table 33), which is the same as that observed in the OCS Heart EXPAND trial.

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

Table 33: Primary Safety Endpoint and Listing of HGRSAEs by Type for the Combined Cohort of OCS Heart EXPAND Trial and OCS Heart EXPAND CAP (N=116)

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

All incidences of PGD were adjudicated by the Medical Monitor. FDA's Panel Executive summary includes comments on the Medical Monitor (MM) adjudications. TransMedics would like to clarify that, in the OCS Heart EXPAND trial, some site-reported cases of PGD were downgraded by the MM per the protocol and ISHLT definitions but others were upgraded and were therefore included in the safety endpoint. In the OCS Heart EXPAND CAP, there were five cases where the MM disagreed with the site determinations for PGD and in all five cases, the MM upgraded the case to be moderate PGD, in contrast with the investigator determination of no PGD.

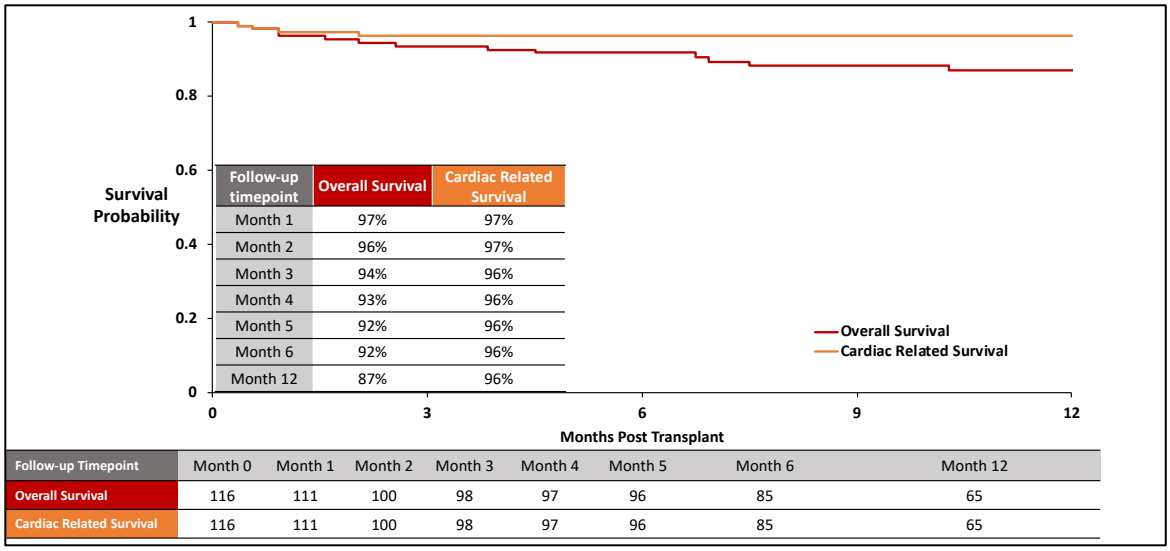
TransMedics performed a sensitivity analyses to determine the impact, if any, of the MM adjudications. The analysis shows that, if the site determined PGD were utilized, the primary endpoint would be met for both the OCS Heart EXPAND trial population (84.0%, p=0.0002) and for the combined OCS Heart EXPAND + CAP population (88.0%, p <0.0001). For the safety endpoint, if the site determined PGD were used instead of the MM adjudicated PGD, the mean number of HGRSAEs would fall to 0.1 ± 0.33, with moderate and severe PGD of 12.1% (14/116) for the combined cohort. This sensitivity analysis demonstrates that the Medical Monitor adjudicated PGD in a balanced manner, consistent with the ISHLT consensus definitions and the protocol and that, regardless of whether the MM adjudications or investigator determinations were used, there was no impact on the assessment of safety or effectiveness of the OCS Heart System.

6.2.12. Patient Survival

Kaplan-Meier overall and cardiac graft-related patient survival for the combined OCS Heart EXPAND + CAP population (116 transplanted patients) is shown in Figure 25 below. Patient survival for OCS Heart EXPAND + CAP patients was 92% at 6 months, and 88% at 12 months.

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

Figure 25: Overall Patient Survival and Cardiac Graft-related Survival for OCS Heart EXPAND Trial and OCS Heart EXPAND CAP Patients Combined through 12 Months Follow-up (N=116)



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

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

The Medical Monitor adjudicated all deaths through 12 months post-transplant. Summary information on the deaths in the combined OCS Heart EXPAND + CAP through 14 months post-transplant is provided in Appendix 3 of this document. There has been one death among the 41 OCS Heart EXPAND CAP subjects. Subject (b)(6) Died on Day 227 from a non-recoverable cerebrovascular event.

6.2.13. Poolability Analyses

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

6.2.14. Serious Adverse Events (SAEs)

Table 34 below shows the adjudicated SAEs by System Organ Class and Preferred term for the combined OCS Heart EXPAND + CAP population of N=116 transplanted recipients. The SAEs are typical of those experienced by heart transplant recipients and there are no signals of concern.

Table 34: List of Adjudicated SAEs By System Organ Class and Preferred Term –Transplanted Recipient Population through 30 Days of Follow-up in Combined OCS Heart EXPAND + CAP Population (N=116)

Status	Subjects (N=116) n (%)	Events n (%)
Total	82 (70.7%)	159 (100.0%)
Blood and lymphatic system disorders	1 (0.9%)	1 (0.6%)
- Anaemia	1 (0.9%)	1 (0.6%)
Cardiac disorders	44 (37.9%)	54 (34.0%)
- Arrhythmia	4 (3.4%)	4 (2.5%)
- Arrhythmia supraventricular	1 (0.9%)	1 (0.6%)
- Atrial fibrillation	8 (6.9%)	8 (5.0%)
- Atrial flutter	1 (0.9%)	1 (0.6%)
- Atrial tachycardia	1 (0.9%)	1 (0.6%)
- Atrioventricular block	1 (0.9%)	1 (0.6%)
- Atrioventricular block complete	2 (1.7%)	2 (1.3%)
- Bradycardia	1 (0.9%)	1 (0.6%)
- Cardiac failure congestive	4 (3.4%)	4 (2.5%)
- Cor pulmonale	2 (1.7%)	2 (1.3%)
- Electromechanical dissociation	1 (0.9%)	1 (0.6%)
- Intrapericardial thrombosis	1 (0.9%)	1 (0.6%)
- Left ventricular dysfunction	8 (6.9%)	8 (5.0%)
- Left ventricular failure	1 (0.9%)	1 (0.6%)
- Nodal rhythm	1 (0.9%)	1 (0.6%)
- Pericardial effusion	5 (4.3%)	5 (3.1%)
- Pericardial haemorrhage	1 (0.9%)	1 (0.6%)
- Right ventricular dysfunction	7 (6.0%)	7 (4.4%)
- Right ventricular failure	1 (0.9%)	1 (0.6%)
- Sinus bradycardia	1 (0.9%)	1 (0.6%)
- Ventricular dysfunction	2 (1.7%)	2 (1.3%)
Congenital, familial and genetic disorders	1 (0.9%)	1 (0.6%)
- Atrial septal defect	1 (0.9%)	1 (0.6%)
General disorders and administration site conditions	1 (0.9%)	1 (0.6%)
- Multi-organ failure	1 (0.9%)	1 (0.6%)

Status	Subjects (N=116) n (%)	Events n (%)
Hepatobiliary disorders	1 (0.9%)	1 (0.6%)
- Hepatic failure	1 (0.9%)	1 (0.6%)
Immune system disorders	15 (12.9%)	15 (9.4%)
- Heart transplant rejection	11 (9.5%)	11 (6.9%)
- Transplant rejection	4 (3.4%)	4 (2.5%)
Infections and infestations	7 (6.0%)	7 (4.4%)
- Bacteraemia	1 (0.9%)	1 (0.6%)
- Clostridial infection	1 (0.9%)	1 (0.6%)
- H1N1 influenza	1 (0.9%)	1 (0.6%)
- Pneumonia	3 (2.6%)	3 (1.9%)
- Sepsis	1 (0.9%)	1 (0.6%)
Injury, poisoning and procedural complications	10 (8.6%)	11 (6.9%)
- Cardiac procedure complication	3 (2.6%)	3 (1.9%)
- Heart injury	1 (0.9%)	1 (0.6%)
- Operative haemorrhage	1 (0.9%)	1 (0.6%)
- Postoperative thoracic procedure complication	1 (0.9%)	1 (0.6%)
- Procedural complication	2 (1.7%)	2 (1.3%)
- Rectal laceration postoperative	1 (0.9%)	1 (0.6%)
- Vascular pseudoaneurysm	1 (0.9%)	1 (0.6%)
- Vena cava injury	1 (0.9%)	1 (0.6%)
Metabolism and nutrition disorders	3 (2.6%)	3 (1.9%)
- Dehydration	1 (0.9%)	1 (0.6%)
- Fluid overload	2 (1.7%)	2 (1.3%)
Nervous system disorders	9 (7.8%)	9 (5.7%)
- Cerebrovascular accident	4 (3.4%)	4 (2.5%)
- Convulsion	2 (1.7%)	2 (1.3%)
- Haemorrhagic stroke	1 (0.9%)	1 (0.6%)
- Neuralgia	1 (0.9%)	1 (0.6%)
- Vocal cord paralysis	1 (0.9%)	1 (0.6%)
Psychiatric disorders	5 (4.3%)	5 (3.1%)

Status	Subjects (N=116) n (%)	Events n (%)
- Delirium	5 (4.3%)	5 (3.1%)
Renal and urinary disorders	22 (19.0%)	22 (13.8%)
- Renal failure acute	19 (16.4%)	19 (11.9%)
- Renal impairment	3 (2.6%)	3 (1.9%)
Respiratory, thoracic and mediastinal disorders	18 (15.5%)	21 (13.2%)
- Acute respiratory distress syndrome	1 (0.9%)	1 (0.6%)
- Acute respiratory failure	2 (1.7%)	2 (1.3%)
- Bronchial secretion retention	1 (0.9%)	1 (0.6%)
- Hydrothorax	1 (0.9%)	1 (0.6%)
- Hypoxia	1 (0.9%)	1 (0.6%)
- Pleural effusion	6 (5.2%)	6 (3.8%)
- Pulmonary oedema	1 (0.9%)	1 (0.6%)
- Respiratory distress	1 (0.9%)	1 (0.6%)
- Respiratory failure	7 (6.0%)	7 (4.4%)
Vascular disorders	7 (6.0%)	8 (5.0%)
- Aortic dissection	1 (0.9%)	1 (0.6%)
- Haematoma	1 (0.9%)	1 (0.6%)
- Haemorrhage	2 (1.7%)	2 (1.3%)
- Hypotension	1 (0.9%)	1 (0.6%)
- Orthostatic hypotension	2 (1.7%)	2 (1.3%)
- Subclavian vein thrombosis	1 (0.9%)	1 (0.6%)

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

6.2.15. Conclusions

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

OCS Heart System Demonstrated Effectiveness:

- An analysis of risk factors for donor hearts from the national UNOS/SRTR registry data demonstrated that the OCS Heart EXPAND and CAP trials enrolled donor hearts that are seldom or rarely transplanted in the U.S. today using ischemic cold storage. The use of the OCS Heart System resulted in successful transplantation of 84% of these types of donor hearts. This finding supports the benefit of the OCS Heart System to expand the donor pool to increase the number of heart transplants performed in the U.S.
- The combined OCS Heart EXPAND + CAP population met the primary effectiveness composite endpoint of 30-day post-transplant patient survival and freedom from severe ISHLT PGD with a 91% success rate on the primary effectiveness composite endpoint.
- The 30-day patient survival of 97% in the combined OCS Heart EXPAND + CAP population is comparable to contemporary standard criteria heart transplant survival in the U.S. (96%; Colvin, et al., 2020).
- The incidence of severe ISHLT PGD of 7.8% in the combined OCS Heart EXPAND + CAP population is lower than contemporary rates of severe heart PGD published in the literature.
- The long-term overall patient survival at 6 and 12 months post-transplant in the combined OCS Heart EXPAND + CAP population was 92% and 87%, respectively. These results are comparable to contemporary overall patient survival rates reported in the UNOS registry for recipients of standard criteria donor hearts preserved on cold storage, i.e., 92% at 6 months and 90% at one year (Colvin, et al., 2020). Post-hoc analysis of cardiac graft-related survival was 96% at 6 month and 12 months post-transplant, respectively.

OCS Heart System Demonstrated Safety:

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

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

- End-stage heart failure is a major public health issue in the U.S. and the incidence is estimated at 650,000 patients annually (Mancini and Colombo, 2015). Heart transplantation is the treatment of choice for addressing end-stage organ failure due to its positive clinical outcomes and excellent quality of life (Stehlik, et al., 2012). Unfortunately, the availability of heart transplantation has been limited by the significant underutilization of DBD hearts due to the limitations of cold static storage. Approximately 7 out of every 10 donated DBD hearts go unutilized in the U.S. due to the limitations of cold storage.
- The use of the OCS Heart System has led to utilization (as defined in the protocol) of a substantial proportion of donor hearts that are seldom used for transplantation today. Simply stated, the OCS Heart EXPAND and CAP trials studied extended criteria donor

hearts that are seldomly used for transplant in the U.S. today and the use of OCS Heart System resulted in transplantation of 81%-84% of these extended criteria donor hearts with good post-transplant outcomes. The utilization of these extended criteria donor hearts using the OCS Heart System has the potential to more than double the annual number of donor hearts available for transplantation in the U.S. The benefits of this increase in the donor pool would be substantial and may enable more life-saving heart transplants to patients dying on the waiting list of end stage heart failure.

6.3. Additional Historical Clinical Experience with OCS Heart System in the U.S. – PROCEED II Trial

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

As described in Section 6.4 of this document, there are fundamental differences between the PROCEED II and OCS Heart EXPAND trials.

6.3.1. Primary Study Endpoint

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

6.3.2. Secondary Study Endpoints

The secondary study endpoints were:

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

6.3.3. Study Populations for Analysis

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

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

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

6.3.4. Subject Disposition

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

6.3.5. Donor and Recipient Baseline Characteristics and Risk Factors

Donor and recipient demographics and risk factors for the OCS and control groups are shown in Table 35 below. The groups were generally well balanced for donor and recipient characteristics.

Table 35: Donor and Recipient Characteristics (As Treated Populations)

Recipient Characteristics	OCS Group (N=62)	Control Group (N=66)
Age (yr)	53.0 (20-71)	54.7 (20-76)
Age > 65	11 (17.4%)	18 (27.3%)
Male Sex	52 (83.9%)	48 (72.7%)
BMI (kg/m^2)	26.3 (17-41)	24.2 (16-38)
Clinical History of Diabetes	17 (27.4%)	17 (25.8%)
On VAD	18 (29%)	15 (22.7%)
Female Donor to Male Recipient	12 (19.4%)	12 (18.2%)

Diagnosis of Cardiomyopathy		
• Ischemic	23 (37.1%)	20 (30.3%)
• Idiopathic	7 (11.3%)	10 (15.5%)
• Dilated Cardiomyopathy	21 (33.9%)	23 (34.8%)
• Congenital Heart Disease	1 (1.6%)	1 (1.5%)
• Restrictive	2 (3.2%)	4 (6.1%)
• Other	7 (11.3%)	9 (13.6%)
UNOS Status • IA • IB • II	 44 (71.0%) 8 (12.9%) 10 (16.1%)	 51 (77.3%) 6 (9.1%) 9 (13.6%)
Donor Characteristics	**OCS Group (N=62)**	**Control Group (N=66)**
Age (yr)	36.2 (18-58)	34.0 (13-60)
Age ≥ 55 years	2 (3.2%)	3 (4.5%)
Male Sex	42 (67.7%)	47 (71.2%)
BMI (kg/m^2)	27.7 (18-44)	26.0 (15-45)
LVEF Mean (range)	60.6 (50-70)	62.0 (45-75)
Cause of Death		
• Anoxia	14 (22.6%)	14 (21.2%)
• Stroke/CVA	17 (27.4%)	18 (27.3%)
• Head Trauma	26 (41.9%)	28 (42.4%)
• Other	5 (8.1%)	6 (9.1%)
Data are mean (range) or number (%), P-values are from the two-sample t-test for continuous variables, testing for a difference in means between treatments, or from Fisher's Exact Test for categorical variables, testing for a difference between treatments in the proportions in each category.		

6.3.6. Primary Endpoint Results

The study met its primary endpoint for all study populations, demonstrating that the OCS Heart System was non-inferior to Control preservation at the pre-specified 10% margin (Table 36).

Table 36: Primary Endpoint (30-Day Patient and Graft Survival and Absence of a Mechanical Assist Device at Day 30) for Various Study Populations

Study Populations	OCS Group	Control Group	Between Group Difference in %	95% Upper Confidence Bound for Difference in %	p-value*
Per Protocol	56/60 (93.3)	59/61 (96.7)	3.4	9.9	0.0469
As Treated	58/62 (93.5)	64/66 (97.0)	3.5	9.6	0.0404

Study Populations	OCS Group	Control Group	Between Group Difference in %	95% Upper Confidence Bound for Difference in %	p-value*
Intent to Treat[1]	63/67 (94.0)	61/63 (96.8)	2.8	8.8	0.0239

Data are number (%).

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

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

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

The study met the secondary endpoint of cardiac graft-related serious adverse events, demonstrating the safety of the OCS for donor heart preservation (non-inferiority of OCS compared with Control). Eight (8) OCS patients and 9 Control patients experienced one or more cardiac graft-related serious adverse events (Table 37).

Table 37: Secondary Endpoint – Patients Experiencing At Least One Cardiac Graft-related Serious Adverse Event (CEC-adjudicated)

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

Data are number (%).

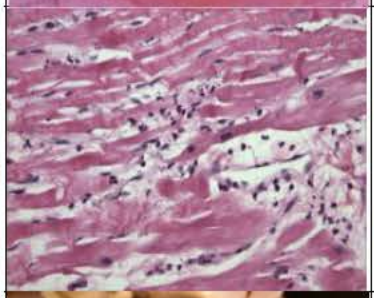
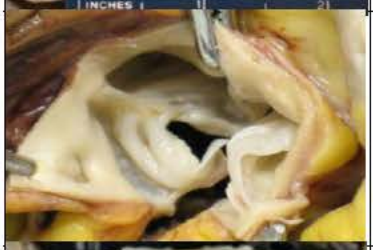
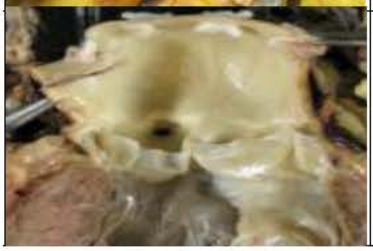
*The non-inferiority hypothesis was demonstrated as the 95% UCB for the difference between the two trial groups was < 10%.

6.3.8. Turned Down Donor Hearts Preserved on OCS

During the conduct of PROCEED II trial, 5 donor hearts preserved on OCS were deemed not acceptable for transplantation while on the OCS and were turned down for transplantation. Four (4) of the 5 donor hearts were declined due to rising perfusate lactate levels during the OCS preservation session, indicating persistent myocardial ischemia despite attempts to optimize myocardial perfusion. One heart was declined due to friable aortic tissue that made it difficult to support the aorta cannula for OCS perfusion. All 5 turned down hearts were examined by independent cardiac transplant pathology core lab. The results of the pathological evaluations are summarized in Figure 26 below. As shown in the figure, 3 out of the 5 hearts (Hearts 3-5) had significant chronic anatomical abnormalities completely unrelated to the OCS Heart preservation. The remaining 2 hearts had evidence of injuries consistent with cause of death and un-related to the OCS Heart preservation.

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

Figure 26: Summary Pathology Report of Turned Down Hearts in PROCEED II Trial

	**Heart 1:** Areas of myocardial hemorrhage and necrosis consistent with donor history of severe myocardial contusion due MVA with flailing chest wall injury and down time with open CPR
	**Heart 2:** Areas of myocardial scarring and necrosis consistent with Cocaine use and consistent with donor history of downtime and CPR and high doses of inotropic support prior to donor heart retrieval
	**Heart 3:** Significant LV wall hypertrophy with septal thickness >2.3 cm that was overlooked during donor heart retrieval
	**Heart 4:** Congenital fusion of the right and left aortic valve cusps, resulting in moderate AO regurgitation and inability to perfuse donor heart antigrade on OCS
	**Heart 5:** Friable and thinning of the aortic tissue due to congenital tissue disorder (Marfan like disorder in the donor)

NOTE: In the FDA's Panel Executive Summary, FDA has inferred that OCS Heart System may have caused injury to the donor hearts being turned down for transplant. We respectfully disagree with FDA's clinical interpretation of the pathology reports. The OCS Heart System could not have caused the above chronic anatomical abnormalities of severe LVH (>2.3 cm), calcified fusion of aortic valves causing aortic regurgitation, and the Marfan like syndrome connective tissue disease.

6.3.9. Summary of Patient Deaths in PROCEED II

There were 6 deaths in the OCS arm and 2 deaths in the control arm during the first 60 days post-transplant. A summary of the causes of death of all 8 patients are described in Table 38 below. The causes of death among these 8 patients were:

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

Table 38: Summary of Patient Deaths during PROCEED II Trial

Subject ID	Group	Days Post-Transplant	Summary
(b)(6)	Control	13	The recipient was a 32 year-old female with restrictive cardiomyopathy. The recipient was urgency status 2 at day of transplant. The subject was not on mechanical circulatory support prior to transplant. The site reported cause of death was primary graft failure. The recipient was unable to wean off cardiopulmonary bypass due to severe RV dysfunction, requiring ECMO support and subsequent cerebral hematoma. The CEC adjudicated the cause of death as cerebral hematoma.
(b)(6)	Control	25	The recipient was a 59 year-old female with dilated cardiomyopathy, urgency status 1A. The subject had IABP support, pre-transplant; however, no other mechanical circulatory support prior to transplant. No surgical complications were reported. An Echo was performed post-transplant. The left ventricle was small but normal LV systolic function with a LVEF of 67%. Normal wall thickness. Normal right ventricular size and mildly depressed right ventricular systolic function. The left and right atrium were mildly dilated. No mechanical circulatory support treatment was administered to the subject. The CEC adjudicated the cause of death to be acute subarachnoid hemorrhage.
(b)(6)	OCS	5	OCS Heart Perfusion Parameters: • Starting lactate on OCS 3.15 – Ending lactate on OCS = 2 mmol/L • OCS perfusion time= 249 mins • Post-OCS ischemic time = 122 mins. The recipient was a 55-year-old male with Rheumatic heart valve disease, urgency status 2. Recipient had history of aortic and mitral valve replacement, which was redone, and biventricular ICD. Early in the transplant procedure the patient experienced signs of allergic reaction to infusion of fresh frozen plasma that was treated initially with Benadryl.

Subject ID	Group	Days Post-Transplant	Summary
			Despite the treatment, the patient experienced bilateral urticarial and hives on lower extremities, transfusion was stopped and IV Solumedrol was given. During weaning off the cardiopulmonary bypass, the donor heart function was noted to be in good condition and the weaning process was initiated. Upon the administration of the heparin reversing agent Protamine, the patient became unstable hemodynamically with sudden deterioration of cardiac function, that was unresponsive to epinephrine boluses. In addition, increased bleeding was noted. Cardiopulmonary bypass was reinitiated. Echo assessment of the heart revealed several clots formation in the RV and LV, as well as the aorta. Clinical diagnosis of Protamine reaction was established. The CEC adjudicated the cause of death to be multi-organ failure secondary to diffuse thrombosis due to protamine reaction on CPB
(b)(6)	OCS	3	OCS Heart Perfusion Parameters: • Starting lactate on OCS 2.26 – Ending lactate on OCS = 2.14 mmol/L • OCS perfusion time= 254 mins • Post-OCS ischemic time = 91 mins. The recipient was a 49-year-old male with dilated cardiomyopathy, urgency status 2. The subject failed to wean off cardiopulmonary bypass despite prolonged reperfusion to regain cardiac rhythm/function. Excessive bleeding requiring 2 hours of surgical hemostasis in the OR. Patient was placed on ECMO for support followed by a surgical attempt to implant a total artificial heart on post-operative day 3, when the patient expired. The CEC adjudicated the cause of death to be hyperacute rejection based on the pathology report from the core lab.
(b)(6)	OCS	3	OCS Heart Perfusion Parameters: • Starting lactate on OCS 2.3 – Ending lactate on OCS = 1.6 mmol/L • OCS perfusion time = 112 mins • Post-OCS ischemic time = 29 mins. The recipient was a 64-year-old female with ischemic cardiomyopathy, urgency status 1B. The patient was unable to wean off cardiopulmonary bypass post-transplant and required ECMO support. On post-operative day 1, the caval anastomosis was ruptured resulting in massive bleed and tamponade requiring reoperation, multiple transfusions and coagulopathy. The CEC adjudicated the cause of death to be bleeding/coagulopathy.
(b)(6)	OCS	5	OCS Heart Perfusion Parameters: • Starting lactate on OCS 4.1 – Ending lactate on OCS = 3.9 mmol/L • OCS perfusion time = 180 mins • Post-OCS ischemic time = 43 mins.

Subject ID	Group	Days Post-Transplant	Summary
			The recipient was a 61 year-old male with ischemic cardiomyopathy, urgency status 1A. The subject was on VAD support for 3 months pre-transplant. Surgery was complicated by dense mediastinal adhesions, severe bleeding/coagulopathy, vasoplegia and unresponsive metabolic lactic acidosis despite supranormal cardiac indices. Dialysis was the only method to clear the lactic acidoses. The donor heart function was excellent. On post-operative day 2, the cardiac output was 6.9 L/min. No mechanical circulatory support treatment was administered to the subject. The CEC determined that the bleeding/hemorrhage resulted in severe lactic acidosis secondary to vasoplegia, pulseless electrical activity (PEA) arrest and ultimately multi-organ failure.
(b)(6)	OCS	33	OCS Heart Perfusion Parameters: • Starting lactate on OCS 1.5 – Ending lactate on OCS = 1.6 mmol/L • OCS perfusion time = 260 mins • Post-OCS ischemic time = 93 mins. The recipient was status 1A male diagnosed with ischemic cardiomyopathy on BiVAD support prior to transplant for 5+ months. Additional medical conditions included hypertension, hyperlipidemia and antiphospholipid antibody syndrome (autoimmune disease). Post-operative course was complicated with bleeding requiring surgical re-exploration. Patient was discharged on Day 13 post-transplant. Discharge echocardiogram indicated LVEF 64% and mild LV hypertrophy. Patient presented to the ER two days later with palpitations. During exam in ER, patient experienced bradycardia and arrested. Echo revealed pleural effusion with cardiac tamponade. Emergent bedside pericardiocentesis was done and patients was brought to OR. Neurology showed anoxic cerebral injury. Patient died on Day 33 post-transplant. Site reported cause of death was hemorrhage per the UNOS database.
(b)(6)	OCS	38	OCS Heart Perfusion Parameters: • Starting lactate on OCS - 3 – Ending lactate on OCS = 4 mmol/L • OCS perfusion time = 124 mins • Post-OCS ischemic time = 66 mins. The recipient was a 69-year-old, status 1A, male diagnosed with ischemic cardiomyopathy. The patient was on VAD support prior to transplant for 5+ months. Additional medical conditions included diabetes, hypertension, hyperlipidemia, hypothyroidism and advanced COPD. Day 7 echocardiogram indicates LVEF 60%, normal LV wall motion. Patient experienced acute renal failure on Day 3 post-transplant, respiratory failure on Day 12 post-transplant and sepsis secondary to respiratory infection on Day 15 post-transplant. The patient died on Day 38 post-transplant. The site reported cause of death was Multiple Organ Failure per the UNOS database.

6.3.10. Overall Adverse Events

The incidence of adverse events was similar between the OCS and Control groups, and there were no statistically significant or clinically meaningful differences between the two groups.

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

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

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

Post-hoc analysis of long-term survival data for PROCEED II subjects from the UNOS/SRTR heart transplant registry indicated that the OCS arm had 19 deaths vs. 11 in the Control arm (Figure 27). The majority of this apparent difference in survival was not related to the cardiac graft. The number of patients whose cause of death was related to the cardiac graft (non-immunologic or immunologic) was the same for the two groups (4 patients in the OCS Group and 4 in the Control Group) through 5 years.

When considering the causes of death for subjects who died > 60 days post-transplant, the higher number of deaths that occurred in the PROCEED II trial is primarily due to a higher incidence of late infection in the OCS arm compared to control (Figure 28).

Using available UNOS/SRTR data, there were 5 patients in the OCS group whose cause of death was late Infection (> 180 days post-transplant); these patients died from a minimum of 197 days to a maximum of 1,737 days post-transplantation. None of these patients had an infection SAE or AE in the 30 days following transplant. Therefore, it is most likely that the infections were not associated with the preservation method, but rather with the immunosuppressed condition of these recipients.

Figure 27: PROCEED II Kaplan-Meier for Overall and Cardiac Related Survival through 5 Years Post-Transplant

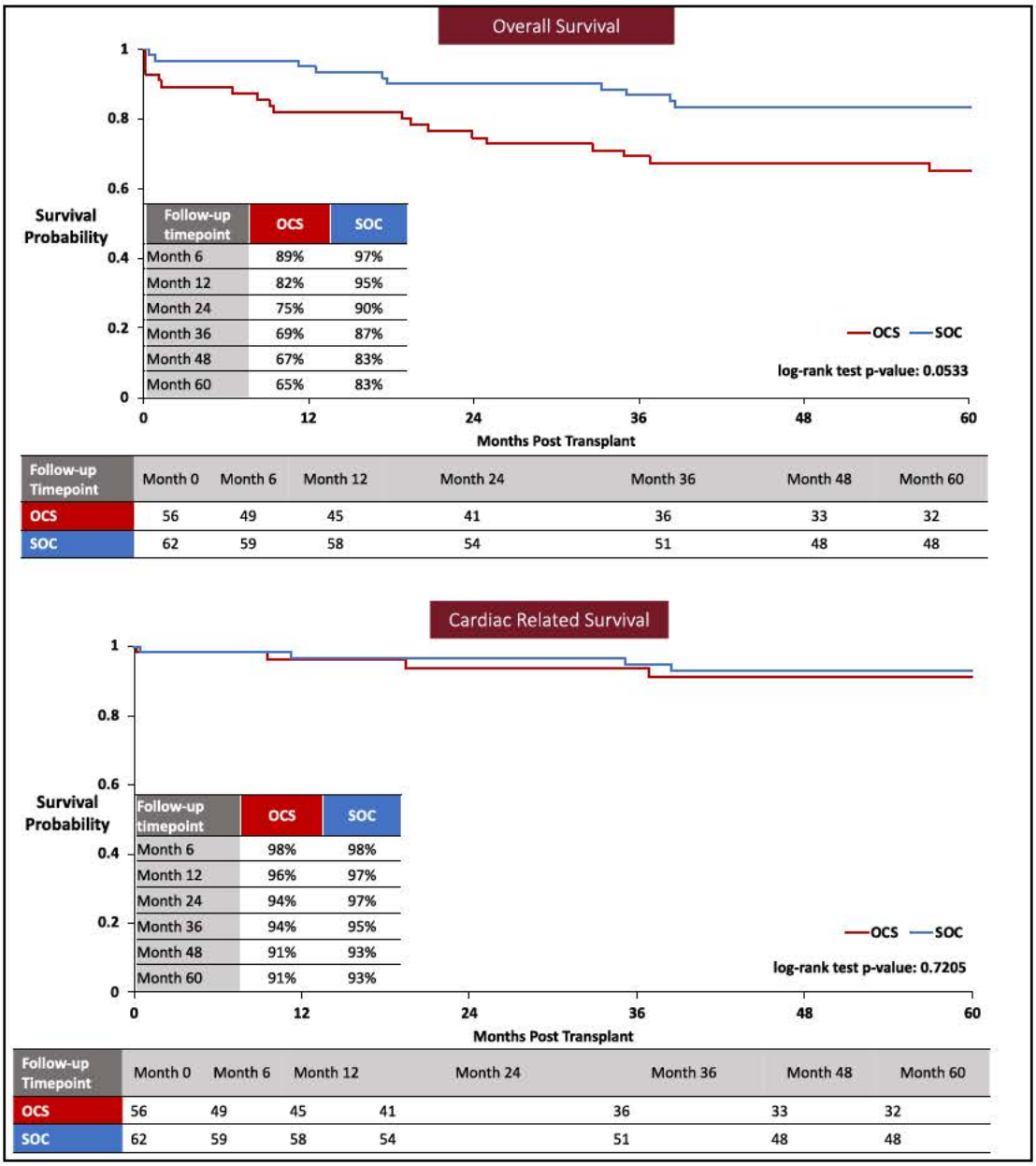
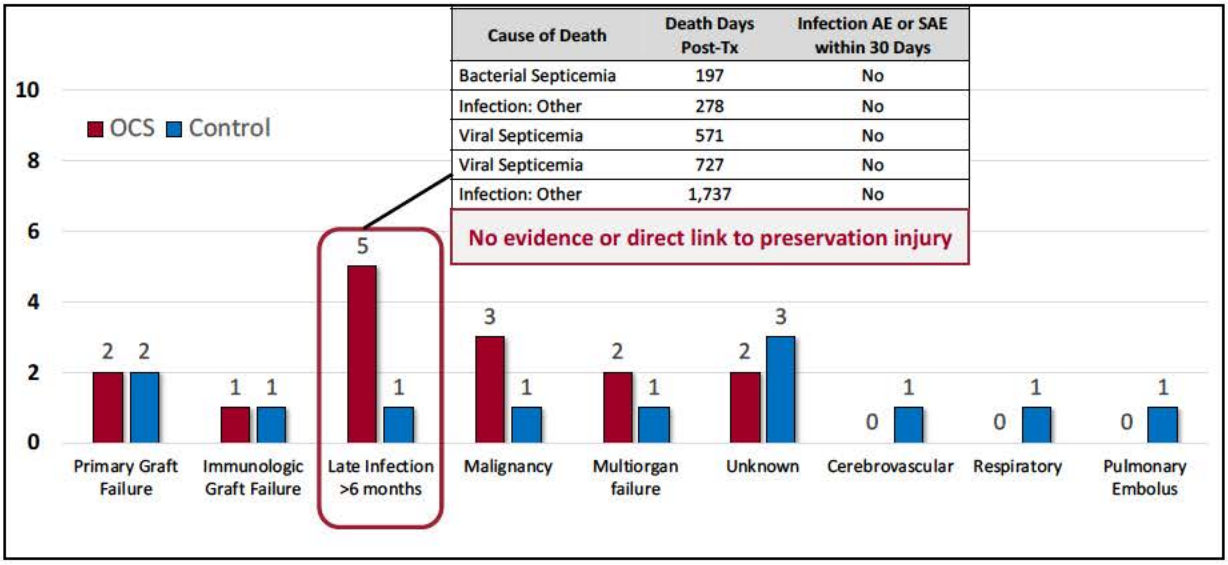


Figure 28: Causes of Death for PROCEED II Subjects > 60 Days Post-transplant from UNOS Database



Cause of Death	Death Days Post-Tx	Infection AE or SAE within 30 Days
Bacterial Septicemia	197	No
Infection: Other	278	No
Viral Septicemia	571	No
Viral Septicemia	727	No
Infection: Other	1,737	No

No evidence or direct link to preservation injury

In addition, four patients died of Malignancy (3 in the OCS group and 1 in the Control group) which is consistent with the UNOS reported causes of deaths for adult heart transplant recipients in the U.S. and is often attributed to the immunosuppressed state of these recipients. Similar trends are reported for the UNOS/SRTR registry in which infection and malignancy are among the leading causes of death post-transplantation among adult heart recipients (Colvin, et al, 2020).

TransMedics acknowledges the increased long-term mortality observed in the OCS group in the PROCEED II trial; however, we have carefully considered these data and we found no clear link to the OCS Heart System or to the preservation period, based on the following facts:

- Cardiac-related mortality is similar between the two groups.
- Most of the long-term deaths were due to non-cardiac-related causes, typical of heart transplant recipients.
- All mortalities in the OCS group that occurred within the initial 60 days post-transplant had an uneventful OCS perfusion and preservation session with stable or declining lactate levels on OCS indicating adequate myocardial protection while on OCS.
- This discrepant mortality signal was not reported or observed in any published study of OCS clinical use for any donor heart criteria (standard, extended and DCD donors). Rather, several peer-reviewed studies from different single and multi-center clinical experience were published reporting better survival results for recipients of donor hearts preserved on the OCS Heart System from standard, extended criteria and even DCD donors (see Section 6.5).

It is important to recognize that the results from PROCEED II are less relevant to the current device and the proposed indication being sought in this PMA. This position is based on the following major fundamental differences between the PROCEED II and OCS Heart EXPAND trials, as well as differences in the OCS Heart System device design and clinical use models evaluated in the OCS Heart EXPAND and PROCEED II trials:

- **Differences in Donor Heart Characteristics:** PROCEED II was a study of standard criteria donor hearts per the early 2000's standards, while the OCS Heart EXPAND trial is a study of extended criteria donor hearts based on 2014 contemporary DBD criteria, i.e., those that are seldom transplanted due to limitation of cold storage and that would benefit from OCS Heart System perfusion.
- **Differences in OCS Heart System Design:** Following completion of the PROCEED II trial, two major device modifications were made and were implemented in the OCS Heart EXPAND trial in order to standardize management of the donor heart perfusion pressure and to minimize the impact of the user learning curve on the use of the OCS Heart System.
- **Differences in Post-OCS Heart Perfusion Myocardial Protection Protocol:** PROCEED II was the first pivotal trial conducted of the OCS Heart System and at the time that the protocol was designed and approved by the FDA, TransMedics and the trial investigators did not fully appreciate the importance of standardizing and controlling the myocardial protection protocol following OCS Heart perfusion after the heart had been removed from OCS. These aspects of the clinical use model were standardized across all investigational sites in the OCS Heart EXPAND trial and are standard practice in current commercial use of the OCS Heart System outside of the U.S.

The section that follows illustrates these fundamental differences between the OCS Heart EXPAND trial and the PROCEED II trials in more detail.

6.4. Differences Between PROCEED II and OCS Heart EXPAND Trials

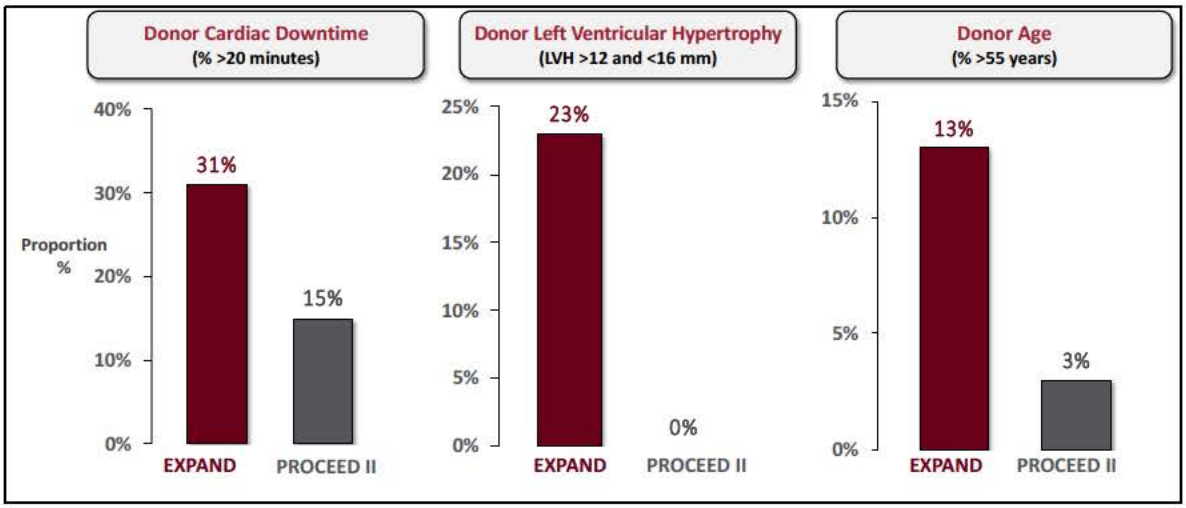
Recognizing the significant clinical unmet need to overcome the limitations of cold static storage on donor heart utilization, the OCS Heart EXPAND trial was designed primarily to demonstrate increased utilization of extended criteria donor hearts, those rarely used for transplantation due to the limitations of cold storage. Therefore, the OCS Heart EXPAND trial differed from PROCEED II trial in its design, objectives, and target donor population. In addition, even though the target recipients for both trials were typical patients on the heart transplant waiting list, clinical practice for heart failure patients had changed over the years, leading to substantial differences in the clinical characteristics of recipient population, particularly in the use of pre-transplant VADs which is known to negatively impact post-transplant outcomes.

And, while PROCEED II is randomized and the OCS Heart EXPAND trial is a single arm study, PROCEED II enrolled fewer OCS patients (62 patients) compared to the 116 patients transplanted in OCS Heart EXPAND trial and OCS Heart EXPAND CAP (and PROCEED II was designed with a 30-day endpoint, while the OCS Heart EXPAND trial has 1-year follow-up pre-specified in the protocol.

6.4.1. Differences in Donor Characteristics and Risk Factors

The differing objectives of the two trials led to significant differences in the donor hearts that were preserved and transplanted in PROCEED II and EXPAND as shown in Figure 29 below.

Figure 29: Comparison Between Donor Characteristics OCS Heart EXPAND vs. OCS Heart PROCEED II Trials



These differences in donor characteristics and risk factors are further supported by the significantly different UNOS Donor Match Run data observed for PROCEED II that showed a mean of 11.8 refusals (median 2) prior to being accepted into the study compared to a mean of 65.6 (median 29) for the OCS Heart EXPAND trial (Table 39). These data show that donor hearts in the OCS Heart EXPAND trial were extended criteria and differed from the donor hearts in the PROCEED II trial.

Table 39: Comparison of UNOS Donor Match Run Data for OCS Heart EXPAND and PROCEED II

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

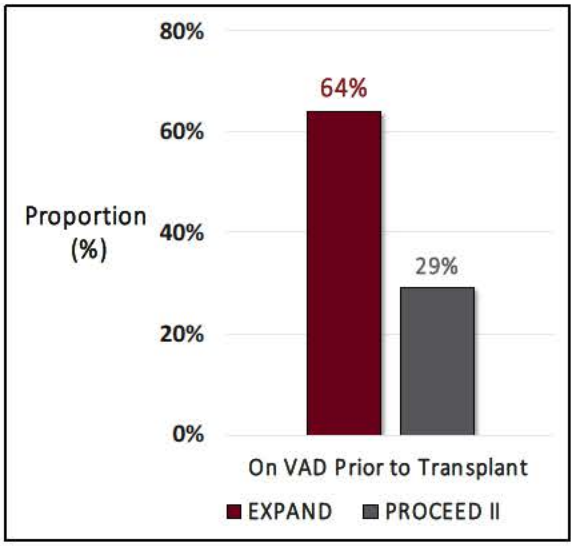
6.4.2. Differences in Recipients

PROCEED II was conducted in 2008-2013, while OCS Heart EXPAND trial was conducted in 2015-2018 and reflects the current clinical practices in the treatment of heart failure, as well as contemporary practices in heart transplantation.

Significant differences were observed between the recipient characteristics for PROCEED II and OCS Heart EXPAND. This reflects not only the difference in inclusion/exclusion criteria between the two trials, but also some of the changes that have taken place in the clinical care of patients with heart failure since the PROCEED II trial was originally designed. For example, in PROCEED

II, only 29% of subjects were on VADs prior to transplant, compared to 64% of subjects in OCS Heart EXPAND. This reflects the changing practice with regard to VAD implantation (see Figure 30 below).

Figure 30: Comparison between Recipients' VAD Use OCS Heart EXPAND vs. OCS Heart PROCEED II Trials



6.4.3. Differences in Device Design and Myocardial Protection Protocols for Post-OCS Heart Perfusion

PROCEED II was the first trial conducted of the OCS Heart System or any other extracorporeal perfusion devices for donor organs. At the time that the protocol was designed and approved, TransMedics and the trial investigators did not fully appreciate the importance of standardizing and controlling various aspects of the clinical use model, including myocardial protection following OCS Heart perfusion. These aspects of the clinical use model were standardized across all investigational sites in the OCS Heart EXPAND trial, as shown in Table 40 below.

In addition, following completion of PROCEED II, two major device modifications were made to standardize OCS Heart management, minimize user learning curve variability on heart perfusion management and increase the ease of use of the OCS Heart System, which were implemented in the OCS Heart EXPAND trial. These device changes were:

- The addition of a fully integrated software controlled IV infusion pump to manage vasoactive Adenosine infusion during OCS heart management and to replace the off-the-shelf manual infusion pump used in the OCS Heart System during PROCEED II.
- A change in the oxygenator location in the OCS perfusion circuit and a change to an oxygenator with a built-in heat-exchanger to allow the user to follow a prospective controlled cooling procedure of the OCS-preserved heart for improved myocardial protection post-OCS warm perfusion.

Table 40: Comparison of OCS Heart System and Protocol Implementation Differences for PROCEED II and OCS Heart EXPAND Trials

PROCEED II	EXPAND Trial
▪ Manual management of vasodilators to manage aortic perfusion pressure	▪ Addition of new software closed loop controlled solution delivery system to automatically manage perfusion pressure to a set point
▪ No standard post-OCS myocardial protection cooling protocols	▪ Addition of heat-exchanger to the OCS circuit to cool donor heart to a set point on OCS and prior to reimplantation

In summary, the PROCEED II and OCS Heart EXPAND trials had different objectives and were conducted over different time periods. This led to differences in the trial design, donor hearts preserved and transplanted, and recipient risk profiles, as well as important differences in aspects of the device design and the clinical use model. These substantive differences limit the applicability of data from the PROCEED II trial in consideration of the OCS Heart System for the proposed clinical indications in this application. Peer-reviewed published real-world experience with the OCS Heart System OUS (discussed in Section 6.5 below) in standard, extended, and DCD donor heart criteria, as well as the results of the OCS Heart EXPAND trial and the OCS Heart EXPAND CAP in the U.S. with extended-criteria donor hearts provide substantial evidence for the safety and effectiveness of the OCS Heart System for the proposed indication.

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

There have been several peer-reviewed publications summarizing clinical studies of the OCS Heart System performed outside the U.S., including studies of DCD hearts (Table 41). Long-term survival for patients who received OCS-preserved donor hearts, with follow-up from one to five years, ranged from 86% to 100%, for recipients of standard criteria, extended criteria and DCD donors. These data provide additional support for the finding that cardiac-related deaths were similar between the two groups in the PROCEED II study through 5 years, and that the imbalance in long-term overall survival was attributable to non-preservation-related causes.

Table 41: Summary of Published Studies of the OCS Heart System from 2014-2019

References	Study Design	Results
Koerner, et al., 2014	Prospective, non-randomized, comparison of OCS (N=29) and cold storage (N=130)	Two-year survival for OCS=89% vs 79% for cold storage Primary graft failure for OCS=6.9% vs 15.3% for cold storage

References	Study Design	Results
	Primary endpoint was patient survival at 30 days, 1 and 2 years post-transplant Secondary endpoints were primary and chronic allograft failure, non-cardiac complications and length of hospital stay	Severe acute rejection – OCS=17% vs 23% for cold storage Acute renal failure – 10% for OCS 25% for cold storage Length of hospital stay – 28 days for OCS vs 26 days for cold storage
Tsui, et al., 2015	Retrospective matched control comparison of OCS (N=19) vs cold storage control (N=24)	Survival at 1.5 years OCS =90% vs 83% for cold storage
Messer, 2017	Single-center observational matched cohort study comparing consecutive patients who received transplants of DCD donor heart between February 1, 2015, and March 31, 2017, vs matched recipients who received transplants of DBD donor hearts between February 1, 2013, and March 31, 2017 DCD Hearts on OCS (N=26) vs DBD Hearts on Cold storage (N=26)	Survival at 90 days: OCS/DCD – 92% vs Cold Storage/DBD – 96% Survival at one year: OCS/DCD – 86%, Cold Storage/DBD – 88%
Garcia Saez, 2016 and 2017	DCD hearts on OCS with High-risk recipients (N=7)	86% Survival for OCS with mean 324 days follow-up
Sponga, et al., 2019	Single center experience Extended Criteria Donors, OCS (N=17), Cold storage (N=70)	30-day survival – 100% OCS vs 94% for cold storage 1-year survival –100% OCS vs 82% for cold storage 5-year survival – 100% OCS vs 73% for cold storage
Rojas, et al., 2019	Prospective registry study at two sites. OCS (N=44) vs Cold Storage (N=82)	Ventilation time 7.1 days OCS vs 17.6 days for cold storage ICU stay 14.2 days OCS vs 24.7 days cold storage Post-operative ECMO 18.2% for OCS vs 28.4% for cold storage 30-day survival – 99.6% for OCS vs 91.2% cold storage One-year survival for OCS =88.6% vs 78.2% for cold storage
Chew, et al., 2019	DCD heart transplants on OCS (N=23)	Four-year survival = 95%

7. OVERALL SUMMARY OF CLINICAL DATA TO SUPPORT APPROVAL OF THE OCS HEART SYSTEM

Data from the OCS Heart EXPAND trial and OCS Heart EXPAND CAP provide substantial evidence of the effectiveness, safety, and favorable benefit/risk profile to support the OCS Heart System approval for the proposed clinical indication for use.

OCS Heart System Demonstrated Effectiveness:

- An analysis of risk factors for donor hearts from the national UNOS/SRTR registry data demonstrated that the OCS Heart EXPAND and CAP trials enrolled donor hearts that are seldom or rarely transplanted in the U.S. today using ischemic cold storage. The use of the OCS Heart System resulted in successful transplantation of 81% and 84% of these types of donor hearts. This finding supports the benefit of the OCS Heart System to expand the donor pool to increase the number of heart transplants performed in the U.S.
- The OCS Heart EXPAND trial met its primary effectiveness composite endpoint of 30-day post-transplant patient survival and freedom from severe ISHLT PGD with an 88% success rate on the primary effectiveness composite endpoint ($p<0.0001$). The combined OCS Heart EXPAND + CAP population (N=116) met the primary effectiveness composite endpoint of 30-day post-transplant patient survival and freedom from severe ISHLT PGD with an 91% success rate on the primary effectiveness composite endpoint.
- The 30-day patient survival of 95% in the OCS Heart EXPAND trial is comparable to contemporary standard criteria heart transplant survival in the U.S. The 30-day patient survival of 97% in the combined OCS Heart EXPAND + CAP population is also comparable to contemporary standard criteria heart transplant survival in the U.S. (96%; Colvin, et al., 2020).
- The incidence of severe ISHLT PGD was 10.7% in the OCS Heart EXPAND trial and 7.8% in the combined OCS Heart EXPAND + CAP population. These rates are comparable to or lower than contemporary rates of severe heart PGD reported in the literature.
- The OCS Heart EXPAND trial long-term patient survival at 6 and 12 months post-transplant was 88% and 84%, respectively. Post-hoc analysis of cardiac graft-related survival was 95% at 6 months and 12 months post-transplant, respectively. The long-term patient survival at 6 and 12 months post-transplant in the combined OCS Heart EXPAND + CAP population was 92% and 87%, respectively. Post-hoc analysis of cardiac graft-related survival in the OCS Heart EXPAND + CAP population was 96% at 6 month and 12 months post-transplant, respectively. The overall patient survival results are comparable to contemporary overall patient survival rates reported in the UNOS registry for recipients of standard criteria donor hearts preserved on cold storage, i.e., 92% overall patient survival at 6 months and 90% overall patient survival at one year (Colvin, et al., 2020).
- TransMedics acknowledges the overall survival difference observed in the PROCEED II RCT based on an unplanned, post-hoc analysis of unadjudicated data from the UNOS national heart transplant registry. However, this finding is of lesser importance in

assessing the effectiveness and safety of the OCS Heart System for the proposed indication because of the following:

- The proposed indication for use in this PMA is based on specific categories of donor hearts studied in the OCS Heart EXPAND and OCS Heart EXPAND CAP trials and does not include the hearts that were the subject of PROCEED II trial; and
- The PROCEED II trial differs substantially from the OCS Heart EXPAND trial which makes it clinically less relevant to the assessment of the OCS Heart proposed indication:
  - There are donor and recipient characteristics that are significantly different between PROCEED II and OCS Heart EXPAND (see Section 6.4.1 and Section 6.4.2).
  - There were major differences in the devices and use models evaluated in the PROCEED II and the OCS Heart EXPAND trials (see Section 6.4.3).
- While an overall long-term survival difference is observed in PROCEED II, the cardiac graft-related mortality through 5 years post-transplant was similar between the OCS and control arms, based on 30-day follow-up data from PROCEED II and the causes of death recorded on long-term follow-up in the UNOS registry.
- The observed difference in the PROCEED II RCT has not been reported or observed in any published study for OCS clinical use for any donor heart criteria (standard, extended, and DCD donors). Several peer-reviewed studies from different single and multi-center clinical experiences were published reporting better survival results for recipients of donor hearts preserved on the OCS Heart System from standard, extended criteria and even DCD donors (see Section 6.5).

- TransMedics has proposed a robust post-market registry to continue to expand the short and long-term clinical evidence on the OCS Heart System in the U.S. in the real-world setting. We propose to enroll an additional 175 new cases into the post-approval registry and follow patient and graft survival up-to 5 years post-transplant. The proposed post-market registry is described in Section 9 of this document.

OCS Heart System Demonstrated Safety:

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

use of the OCS to maximize safety for the patients. See Section 8 of this document for a detail description of the training program.

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

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

8. DEVICE TRAINING

TransMedics developed a comprehensive user training program to train organ transplant and retrieval physicians and transplant professionals on the use of the OCS Heart System. Trainees typically include transplant and retrieval physicians, transplant coordinators/nurses, or perfusionists. The training program has evolved over time as experience was gained with the OCS Heart System. An overview of the training program is provided in the sections that follow.

8.1. Training Overview

TransMedics provides the core training, which involves a classroom didactic presentation describing the clinical use model and how to use the device, followed by 1-2 days of hands-on training that requires participation in a laboratory study, using swine hearts, to simulate the clinical use of the OCS Heart System.

TransMedics also provides refresher training for any user/customer that has not used the OCS Heart System in a clinical run for an extended period of time.

8.2. Training Content/Materials

The fundamental approach of training has consistently been based on covering all aspects of clinical use as follows:

- Pre-retrieval readiness and checks for all needed supplies to use the device that includes Heart Console check; run bag check; gas cylinder check; medication; and solution check
- OCS set up (installing the disposables) and device troubleshooting
- Solutions (flush and priming solution) and medication preparation
- System priming and sampling
- Heart cannulation and instrumentation
- Initial stabilization
- Baseline assessment (Monitoring)
- Final assessment (Monitoring)
- Clinical Troubleshooting scenarios
- System cleaning and storage.

In addition, each site receives an iPad® containing a proprietary OCS Heart training and support application that includes step by step instructions of the use model for OCS Heart System, as well as training videos/materials for immediate access.

9. POST-APPROVAL STUDY

TransMedics recognizes the value of collecting post-approval and longer-term data for the OCS Heart technology. TransMedics is proposing a post-approval plan to collect long-term clinical outcome data from additional new patients who will receive a donor heart preserved by the OCS Heart System. In addition, the existing UNOS database will be leveraged to obtain follow-up patient and graft survival data for OCS Heart EXPAND participants. TransMedics believes that collecting long-term data in a post-approval study is a scientifically appropriate and valid approach for an organ preservation device, and will achieve a reasonable balance between pre- and post-market data requirements.

Accordingly, we are proposing a post-approval plan that will have two components:

- Post-Approval registry to collect additional short and long-term clinical outcomes from patients who receive a heart preserved on the OCS Heart System.
- Follow-up of OCS Heart EXPAND participants through the existing UNOS/SRTR database.

9.1. Proposed Post-Approval Observational Registry - OCS Heart Registry

This is a single-arm, prospective, multi-center, observational post-approval registry. Donors and recipients will be consistent with the approved indication for use and will reflect the eligibility criteria of the OCS Heart EXPAND trial.

Patients will be followed 12 months post-transplantation. Patient and graft survival from 24 through 60 months post-transplantation will be evaluated by accessing data from UNOS database.

9.1.1. Primary Endpoint

The primary endpoint is 12-month post-transplant patient freedom from cardiac graft-related death.

9.1.2. Safety Assessment

Incidence of:

- Patient death within 30 days post-transplantation
- Primary graft failure requiring re-transplantation within the initial 30 days post-transplant.

9.1.3. Other Endpoints

- Kaplan-Meier freedom from cardiac graft-related death estimated at Month 1, 12, 24, 36, 48, and 60
- Kaplan-Meier freedom from death due to all causes estimated at Month 1, 12, 24, 36, 48, and 60
- Kaplan-Meier freedom from re-transplantation estimated at Month 1, 12, 24, 36, 48, and 60
- Donor heart utilization rate, defined as the number of eligible donor hearts successfully transplanted divided by the total number of eligible donor hearts preserved on the OCS Heart System.

9.1.4. Statistical Methods for Primary Analysis Population

9.1.4.1. Analysis Populations

The Primary Analysis Population is defined as subjects who meet the recipient eligibility criteria and are transplanted with hearts that meet the donor eligibility criteria. All pre-specified hypothesis testing will be performed on this population when all of these recipients have completed 12 months of follow-up.

All recipients in the registry will comprise the Full Analysis Population. All analyses will also be repeated on the Full Analysis Population when these recipients have completed 12 months of follow-up, except that there is no formal hypothesis testing planned on this population.

9.1.5. Analysis of Endpoints

9.1.5.1. Primary Endpoint

The estimated one-year freedom from cardiac graft-related death for standard criteria donor hearts in the U.S. per the Organ Procurement Transplant Network (OPTN) is 98% by the Kaplan-Meier method (Colvin, et al., 2018). The primary endpoint of the post-approval study is that the 12-month freedom from cardiac graft-related death following transplantation with a donor heart preserved on the OCS Heart System is greater than a performance goal based on the

OPTN estimate and a margin of 12%, resulting in a performance goal of 86% (i.e., 98% - 12% = 86%). The hypothesis is stated below:

H_0: $\pi_{OCS} \leq 86\%$

H_a: $\pi_{OCS} > 86\%$,

where π_{OCS} is the true freedom from cardiac graft-related death for subjects transplanted using the OCS Heart System in the post-approval study and 86% is the performance goal.

Patient survival from cardiac graft-related death will be based on the binomial method (simple proportion) as lost to follow-up/withdrawals are not expected. In order to report the most complete and accurate outcomes in this patient population, the UNOS/SRTR database will be queried for outcomes for missing patients. The primary objective will be met if the lower 90% exact binomial (Clopper-Pearson) confidence bound of the survival proportion exceeds the performance goal.

9.1.5.2. Safety Assessment

The results for the safety assessment will be summarized with descriptive statistics (n, mean, standard deviation, median, minimum, maximum, and 95% confidence interval based on the t-distribution).

9.1.5.3. Other Endpoints

- Freedom from cardiac graft-related mortality through 60 months will be summarized using the Kaplan-Meier method, with survival estimates at 1, 12, 24, 36, 48, and 60 months. Patients not having the event of interest will be censored at the date of last contact in the Kaplan-Meier estimate.
- Freedom from all-cause mortality through 60 months will be summarized using the Kaplan-Meier method, with survival estimates at 1, 12, 24, 36, 48, and 60 months. Patients not having the event of interest will be censored at the date of last contact in the Kaplan-Meier estimate.
- Incidence (simple proportion) of re-transplantation at 1, 12, 24, 36, 48, and 60 months will be calculated along with 95% exact binomial (Clopper-Pearson) confidence intervals.
- Donor Heart Utilization rate, defined as the number of eligible donor hearts successfully transplanted divided by the total number of eligible donor hearts preserved on the OCS Heart System will be summarized with descriptive statistics.

9.1.6. Sample Size Determination

Based on the OPTN data, patient survival from cardiac graft-related death is estimated to be 98% at 12 months. Given that the OCS Heart Registry will be enrolling donor hearts with one or more risk factors and considering the variability of the real-world clinical use environment, a 12% margin is established, resulting in a performance goal of 86%, using the following assumptions:

- Alpha = 0.1

- Power = 80%
- True proportion = 0.93.

A sample size of 135 subjects is required and provides approximately 80% power (with a two-sided alpha level of 0.10) based on the exact method for a single binomial proportion. The sample size is increased to 175 to allow for the potential enrollment of subjects who do not meet eligibility for the primary analysis population.

9.2. Long-Term Follow-up of Existing OCS Heart EXPAND Trial Patients

TransMedics is proposing to collect critical clinical outcomes on existing OCS Heart EXPAND trial patients for up to 5 years from date of heart transplantation by accessing the UNOS/SRTR database. The following analyses will be performed:

- Kaplan-Meier patient survival from cardiac graft-related death (freedom from cardiac graft-related mortality) curves will be generated through 5 years (60 months) post-transplant.
- Kaplan-Meier patient survival (freedom from all-cause mortality) curves will be generated through 5 years (60 months) post-transplant.
- Kaplan-Meier graft survival (freedom from re-transplantation) curves through 5 years (60 months) post-transplant will be generated.

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11. APPENDIX 1: PRINCIPLES OF OPERATION/CLINICAL USE

The OCS Heart System has been designed to be incorporated into the standard of care for contemporary heart transplantation procedures. The principles of operation are described below.

11.1. Preparation and Connection of the Donor Heart to the OCS Heart System

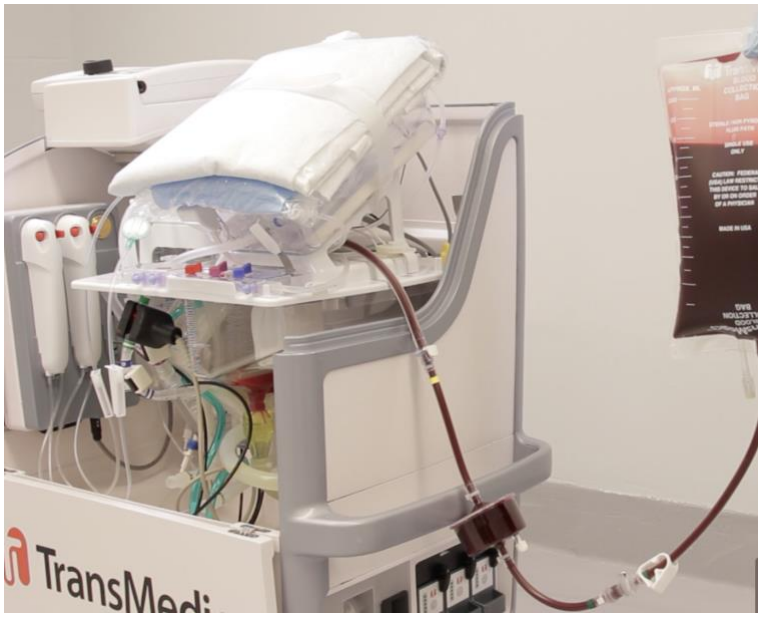
11.1.1. Pre-Retrieval Readiness

An OCS retrieval bag, which contains all supplies necessary for donor heart retrieval, is assembled prior to use. If the donor heart offer is accepted, the team begins routine OCS Heart System checks to insure preparedness for use. During this time, the team will check batteries and gas tank supply. The HPM is supplied pre-assembled, and the team inserts the HPM into the Heart Console, runs the system self-test, and clips the device flow probes and oxygen saturation/hematocrit probe onto the circuit tubing. The SDS cassettes are connected to the respective ports on the HPM.

11.1.2. Collect and Filter Donor Blood

Blood is collected from the heparinized donor, which is passed through a leukocyte-depleting filter and into the reservoir of the HPM, as shown in Figure 31 below.

Figure 31: Donor Blood Collection and Delivery into HPM Reservoir

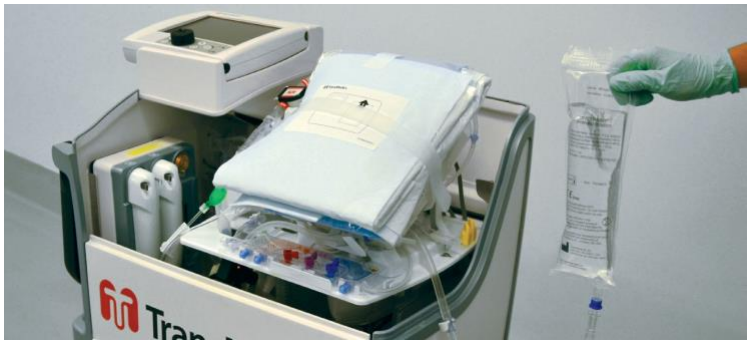


11.1.3. Prime System with Blood and Fluids

The donor blood is supplemented with 500 mL of the OCS Priming Solution, which is added to the reservoir through a prime line as shown in Figure 32 below. These solutions are mixed by starting the Heart Console pump, which also provides perfusate flow through the circuit to prime and de-air the HPM. Starting the pump will automatically activate gas flow and blood

warming. The user adds the recommended additives and uses the Wireless Monitor to enable the delivery of OCS Maintenance Solution.

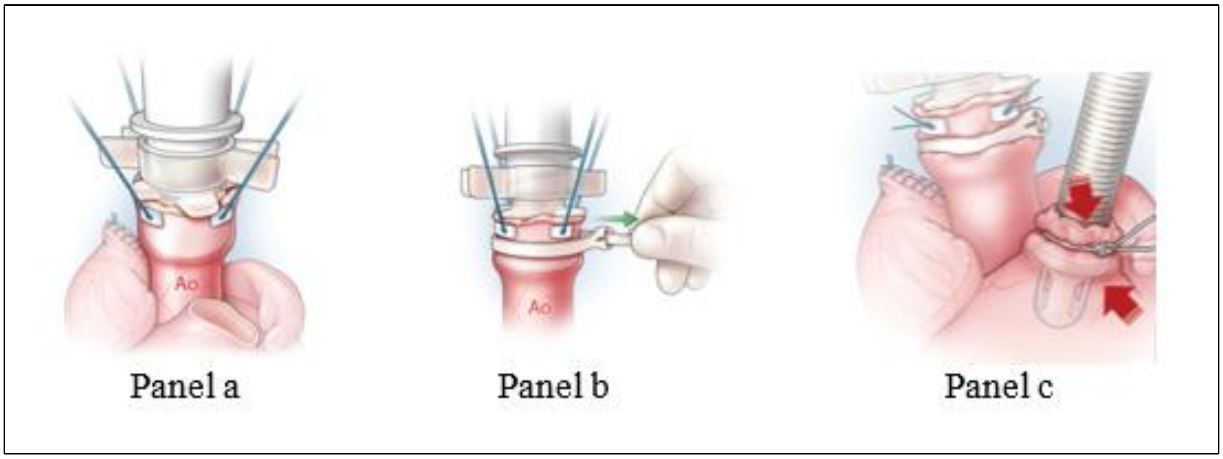
Figure 32: Administration of the OCS Priming Solution into HPM Reservoir



11.1.4. Instrumentation of Donor Heart

Cardioplegia is administered to the donor heart according to the institution's standard procedure, and the surgeon removes the heart in accordance with their institution's standard procedures. The arteries and veins that are not used for OCS are sutured closed. Four hard double-pledgeted sutures are applied to the aorta at the 12, 3, 6, and 9 o'clock positions (Figure 33, Panel a). The appropriately-sized aortic cannula is then inserted into the aorta and secured below the pledgets with a single cable tie (Figure 33, Panel b). A purse string suture is then used for pulmonary artery cannulation and is further secured with umbilical tape (Figure 33, Panel c).

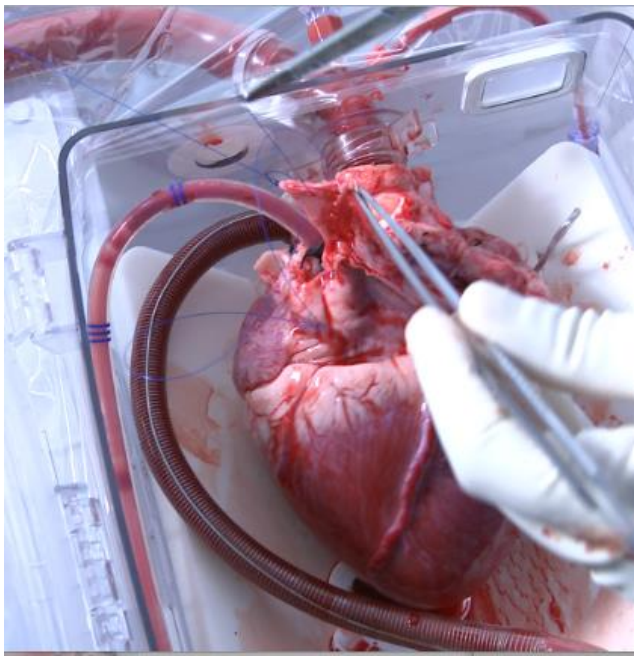
Figure 33: Instrumentation of the Donor Heart on OCS (Panel a, Four hard double-pledgeted sutures; Panel b, Cable Tie; and Panel c, Pulmonary artery cannulation)



The donor heart is connected to the HPM fluid circuit through the use of a disposable aortic connector and the pulmonary artery cannula, provided as part of the HPS. These connections allow for perfusing the heart through the aortic connector and recirculating the perfusate back to the reservoir through the pulmonary artery cannula. The donor heart is instrumented on the OCS in a retroverted orientation (with the posterior facing the user). The superior vena cava is tied off. 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, as shown in Figure 34 below, is

placed to assist with de-airing. The temperature of the heart is gradually warmed as the heart is perfused with the warmed, oxygenated blood that has been already supplemented with OCS Priming Solution. A rhythm is initiated by external defibrillation, if needed.

Figure 34: Left Ventricle Vent



11.2. Maintenance and Transportation of the Donor Heart

The OCS is used to maintain and protect the donor heart during transportation. Pump flow and solution infusion rates are set to optimize coronary flow, aortic pressure, and heart rate. Determination of arterial and venous lactate values are used to confirm adequacy of perfusion of the heart. The OCS can be operated by either external AC power or internal batteries. During transport, the Wireless Monitor will display a number of parameters, including heart rate, pump flow rate, coronary flow rate, aortic pressure, temperature, oxygen saturation (SvO_2), and hematocrit (HCT) levels.

An off-the-shelf portable blood gas analyzer is utilized to check blood chemistry and lactate.

11.3. Evaluation and Transplantation

11.3.1. Evaluate Heart

The heart is evaluated for suitability for transplantation by the heart transplant team (while the heart is on the OCS Heart System), including an evaluation of the preservation conditions and parameters collected by the OCS.

11.3.2. Prepare Recipient

If the donor heart is accepted, the transplantation procedure will proceed.

11.3.3. Arrest Donor Heart

The donor heart is cooled on the system by connection to a standard OR heater/chiller and then arrested by administering a cold cardioplegia solution through the aortic access port of the HPM. At this time, 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 System to implantation of the donor heart.

11.3.4. Remove Heart from Organ Care System

The donor heart is removed from the OCS. The surgeon removes the OCS cannulae and prepares the donor heart for transplantation in accordance with standard surgical procedures.

11.3.5. Transplant into Recipient

The cardiac transplantation procedure continues according to the standard operating procedures at the center.

11.3.6. Post-Device Use

The HPM is removed and discarded. The OCS is cleaned, and the batteries are recharged in preparation for the next use.

12. APPENDIX 2: SUMMARY OF NON-CLINICAL STUDIES

This appendix provides a high-level summary of the non-clinical testing performed to support demonstration of a reasonable assurance of safety and effectiveness of the OCS Heart System. These data have been reviewed by FDA and all outstanding issues and questions have been addressed.

12.1. Engineering Bench Testing

TransMedics has performed a series of engineering studies to demonstrate the OCS Heart System meets its performance specifications, and is safe, suitable and ready for commercial distribution.

Table 42 below identifies the engineering bench testing performed on the OCS Heart System for which we are seeking PMA approval. The testing was performed at the system level, on the OCS Heart System, as well as on the components that comprised of the system, including the Heart Console and Heart Perfusion Module (HPM).

Table 42: Summary of Bench Testing

Test	Conclusion
OCS Heart System Shock and Vibration Testing	The OCS Heart System performed to specification when exposed to levels of mechanical shock and vibration consistent with those anticipated during transport and extended use.
OCS Heart System Operational Temperature and Humidity Testing	The OCS Heart System performed to specification when subjected to an environment presenting the extremes of its rated temperature and humidity ranges. Furthermore, the system successfully completed system functional testing after the exposure.
OCS Heart System Operational Altitude Testing	The OCS Heart System performed to specification when exposed to levels of altitude expected during OCS use.
Operational OCS Heart System Driven Rain Test	This test verified that, after simulating transport of the OCS Heart System in driving rain conditions, the OCS did not suffer loss of function or experience a safety hazard as a result of being subjected to the rain exposure.
ECG Synchronization Mode Verification	The OCS Heart System met the specified acceptance criteria for ECG Synchronization mode.
Heart Console Mechanical Design Verification	The mobile base and the basic attributes of the Wireless Monitor met the specified mechanical requirements for use.
OCS Heart System PCBAs Electrical Test	The TransMedics manufacturing processes include adequate tests to verify that the electrical systems are free from functional defects.
OCS Battery Pack Life Cycle Test	The OCS battery packs met all specifications through their expected life and are acceptable for use in the OCS Heart System.
Wireless Monitor Battery Life Cycle Test	The Wireless Monitor battery packs met all specifications through their expected life and are acceptable for use.

Test	Conclusion
Heart Console SvO_2/HCT Probe Accuracy Test	The Heart Console probe that measures oxygen saturation and Hematocrit is acceptable for use in the specified ranges of HCT and SvO_2.
Heart Console Bluetooth Serial Adapter Performance Verification	The Heart Console Bluetooth module met the OCS Heart System product requirements for wireless communication and range.
Heart Console Gas Cylinder Regulator Performance and Reliability Verifications	The Gas Cylinder Regulator met the defined OCS safety and reliability requirements. The Gas Regulator also met the defined performance requirements with regard to the specified ranges of gas flow rates and gas cylinder pressures.
Heart Console Flowmeter Board Verification	The boards in the Heart Console that are used to measure perfusate flow in the HPM met the OCS product requirements with respect to flow rate range and accuracy.
Heart Console Gas Cylinder Retention Strap Verification	The verification proved proper fit and retention of gas cylinder within the Heart Console's gas cylinder compartment.
HPM Front End Board Verification	This test verified that the Printed Circuit Board Assembly (PCBA) on the HPM Front End Board met product requirements.
HPM Heater Plate and Blood Temperature Sensor Accuracy	This test verified the accuracy of the sensors that measure blood temperature and heater plate temperature in the HPM.
HPM Reservoir Blood Defoaming Test	This test verified the ability of the perfusate reservoir in the HPM to filter foam under challenged conditions.
HPM Reservoir Filter Effectiveness	This test verified that the filtration efficiency of the perfusate reservoir met the product specification.
Aorta Cannula Performance Verification	These tests verified the ability of the heart cannulation accessories within the HPS to adequately retain aortas.
HPM Pressure Transducer Accuracy Verification	This test verified the accuracy of the pressure transducer used on the HPM.
HPM Oxygenator Performance Testing	The oxygenator used in the HPM, the Maquet QUADROX-i small adult oxygenator, was verified to meet the HPM performance specifications.
Tensile Strength of HPM Tubing Connections	The results demonstrate the tensile and mechanical integrity of all HPM tubing and connectors used to transport perfusate or gas.
SDS Cassette Life Testing	The SDS disposable cassettes were verified to meet specification for its specified operational life.

12.2. Biocompatibility Testing

TransMedics performed a series of biocompatibility studies to demonstrate the safety, suitability, and compatibility of the materials of the HPS, which consists of the HPM and HPS Accessories. These studies were selected and performed in consultation with international recognized safety standards. All studies cited here were conducted in compliance with 21 CFR Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies (GLPs).

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

Biocompatibility tests and results are provided in Table 43 below.

Table 43: Biocompatibility Testing Summary for HPS

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

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

12.3. Software Verification and Validation Testing

TransMedics performed system level software verification and validation testing to demonstrate the OCS Heart System performs as intended. The device passed all testing, met its requirements, and is safe, suitable, and ready for commercial distribution. Software documentation was provided in accordance with the FDA guidance entitled, "Guidance for the Contents of Premarket Submissions for Software Contained in Medical Devices." Verification and validation testing included unit tests, static analysis, system level verification tests (which included functional testing to demonstrate the device met its requirements), code review, and validation testing.

12.4. Cybersecurity

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

To address potential cybersecurity risks, TransMedics provided information according to FDA guidance entitled, "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices." This information included, among other things, a Cybersecurity Threat Model and Assessment, validation/verification testing (which included penetration testing), and a plan for identifying and responding to emerging cybersecurity issues. Collectively, this information demonstrated that TransMedics has appropriate controls in place to identify, protect, detect, respond, and recover from cybersecurity threats per the FDA guidance.

12.5. Electrical and Medical Device Safety

The OCS Heart System was tested to demonstrate that it meets the requirements for medical device safety, including electrical safety. The system was tested by an outside laboratory according to the Edition 3.1 of the IEC 60601-1 standard, as well as the ANSI/AMMI and CSA versions of the standard. The OCS Heart System met the requirements of the standards. Results are shown in Table 44 below.

Table 44: Summary of the Test Results for Electrical, Thermal, and Mechanical Safety

Test Description	IEC/ANSI/AAMI 60601-1: 2005 +A1:2012 Clause	Result
General Requirements	4	Pass
General Requirements for Testing ME Equipment	5	Pass
Classification of ME Equipment and ME Systems	6	Pass
ME Equipment, Identification Marking and Documents	7	Pass
Protection Against Electrical Hazards from ME Equipment	8	Pass
Protection Against Mechanical Hazards of ME Equipment and ME Systems	9	Pass
Protection Against Unwanted and Excessive Radiation Hazards	10	Pass
Protection Against Excessive Temperatures and Other Hazards	11	Pass
Accuracy of Controls and Instruments and Protection Against Hazardous Outputs	12	Pass

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

12.6. Electromagnetic Compatibility (EMC)

The OCS Heart System was tested to demonstrate that it meets the requirements for radio frequency emissions and radio frequency susceptibility (together, EMC). The system was tested by an outside laboratory according to standards for EMC requirements of electrical equipment (IEC 60601-1-2 (4th edition) – Group 1, Class A, non-life supporting equipment, CISPR 25, and RTCA DO-160G). The OCS Heart System met the requirements of the standards. Results are shown in Table 45 below.

Table 45: Summary of the Emission and Immunity Testing

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

12.7. Wireless Technology

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

12.8. Sterilization

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

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

12.9. Shelf Life Testing

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

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

12.10. Animal Functional Testing

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

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

The testing demonstrated that the OCS Heart System adequately maintained and perfused the donor heart on the OCS when used in accordance with the current use model. The hearts were adequately maintained and perfused on the OCS Heart System according to the predefined protocol and perfusion parameters. The metabolic profile met the acceptance criteria of a stable trend throughout perfusion and a trend of neutral or absorbing venous-arterial differential. All acceptance criteria were met.

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

13. APPENDIX 3: OCS HEART EXPAND TRIAL DEATH NARRATIVES

All reported deaths that occurred in the OCS Heart EXPAND trial and OCS Heart EXPAND CAP have been reviewed and adjudicated by the Medical Monitor. A summary of the deaths that occurred through 12 months post-transplant are provided in Table 46, and full narratives of each death are provided in the section that follows.

Table 46: Summary of Deaths in the OCS Heart EXPAND + CAP Trials through 12 Months Post-transplant

Patient ID	Site Reported Cause of Death	Adjudicated Primary Cause of Death	Within 30 Days	Initial In-hospital Death	Post-discharge Death
(b)(6)	Myocyte Necrosis – Multi Organ Failure	Myocyte Necrosis and Multi-Organ Failure Secondary to Biventricular Dysfunction	29 days		
(b)(6)	Multiple Organ Failure	Multiple Organ Failure Secondary to Primary Graft Dysfunction	12 days		
(b)(6)	Multi-Organ Failure	Multiple Organ Failure Secondary to Pre-existing Liver Cirrhosis	29 days		
(b)(6)	Primary Graft Dysfunction	Primary Graft Dysfunction	18 days		
(b)(6)	Acute Respiratory Distress Disease	Acute Respiratory Distress Disease		80 days	
(b)(6)	Multi-Organ Failure	Multi-Organ Failure[1]		49 days	
(b)(6)	Unknown, Possible Complication of Endocarditis	Multi-Organ Failure and Endocarditis[2]			138 days
(b)(6)	Severe Hypoxic Ischemic Encephalopathy	Severe Hypoxic Ischemic Encephalopathy Secondary to Pulmonary Embolism			119 days
(b)(6)	Multi-Organ Failure	Multi-Organ Failure Secondary to Primary Graft Dysfunction			64 days
(b)(6)	Sepsis, Pneumonia	Sepsis, Pneumonia			314 days
(b)(6)	Re-Occurring Amyloidosis with Refractory GI Bleed	Re-Occurring Amyloidosis with Refractory GI Bleed			212 days
(b)(6)	Septic shock	Multifactorial septic shock following acute rejection			205 days
(b)(6)	Non-recoverable cerebrovascular event	Non-recoverable cerebrovascular event			227 days

(1) Subject had severe vasoplegia post-transplant that led to Multi-organ failure.

(2) Subject had surgical PA anastomotic complication leading to acute RV outflow obstruction, RV dysfunction, ECMO use and ultimately led to Multi-organ failure.

13.1. Patient ID (b)(6)

Donor History (UNOS ID (b)(6) A 55-year-old female donor that died due to a cerebrovascular hemorrhage. Donor did not have any notable medical history. The donor angiogram did not display any abnormal findings, while the donor echo noted mild tricuspid and mitral regurgitation.

Recipient History: A 68-year-old, status 1B, male diagnosed with ischemic cardiomyopathy. The patient was not on mechanical circulatory support prior to transplant but was noted to not be a good candidate for VAD due to refractory ventricular tachycardia. An ICD was placed prior to transplant.

Retrieval and OCS Perfusion: The donor heart was accepted into the trial because of an expected total cross-clamp time ≥ 2 hours with a donor age ≥ 55 years. The donor heart was surgically retrieved on (b)(6) and perfused on the OCS Heart System. Perfusion trends of the donor heart were stable throughout preservation on the OCS Heart System and met implantation criteria per protocol definition and clinical judgment (as seen in Table 47).

Table 47: OCS Perfusion Parameters and Lactate of Donor Heart

OCS Parameters/Session	
Baseline Donor Arterial Lactate	0.93 mmol/L
Pre-Instrumentation Lactate on OCS	0.55 mmol/L
Initial Arterial Lactate on OCS Initial Venous Lactate on OCS	1.17 mmol/L 1.21 mmol/L
Final Arterial Lactate on OCS Final Venous Lactate on OCS	2.54 mmol/L 2.52 mmol/L
Total OCS Perfusion Duration (time)	228 min
Donor Heart Out of Body Time	327 min

Recipient Outcome: The recipient underwent heart transplantation on (b)(6). The subject was diagnosed with Severe PGD-LV during the first 24 hours post-transplant per protocol due to VA-ECMO placement.

The patient's post- transplant course was complicated by the following SAE:

- Myocyte necrosis and T Lymphocyte Rejection Secondary to Biventricular Dysfunction.

On (b)(6), the patient underwent chest washout, IABP placement and endocardial biopsy. The biopsy demonstrated significant myocyte necrosis with patchy viable myocardium and microvascular infiltrates. Notes indicated that the myocyte necrosis may be more suggestive of ischemic/preservation injury; however, cellular rejection could not be excluded based on the inflammatory infiltrates. The subject was subsequently treated for cellular rejection and plasmapheresis on POD #9, #11 and #13. The subject then struggled with multiple infections, AK requiring CRRT, GI bleeding, and metabolic encephalopathy. The subject was taken off ECMO on (b)(6) (POD# 14). This event was adjudicated to be an

anticipated heart graft-related event (Severe PGD-LV), possibly related to preservation, and resulting in death.

The patient was never discharged from the hospital following transplantation.

Recipient Death: The patient expired on (b)(6) (29 days post-transplantation) in the hospital. The site-reported cause of death was "Myocyte Necrosis – Multi Organ Failure." The adjudicated cause of death was Myocyte Necrosis and Multi-Organ Failure Secondary to Biventricular Dysfunction.

13.2. Patient ID (b)(6)

Donor History (UNOS ID (b)(6)): A 51-year-old male donor that died due to a cerebrovascular hemorrhage. Donor was noted to be CMV+. The donor angiogram did not display any abnormal findings, while the donor echo noted a septal wall thickness of 13 mm and mild tricuspid regurgitation.

Recipient History: A 47-year-old, status 1A, male diagnosed with dilated idiopathic cardiomyopathy with an LVAD placed on (b)(6)

Retrieval and OCS Perfusion: The donor heart was accepted into the trial because of an expected total cross-clamp time > 2 hours with a left ventricular septal or posterior wall thickness > 12 mm, but < 16 mm. The donor heart was surgically retrieved on (b)(6) and perfused on the OCS Heart System. Perfusion trends of the donor heart were stable throughout preservation on the OCS Heart System and met implantation criteria per protocol definition and clinical judgment (as seen in Table 48).

Table 48: OCS Perfusion Parameters and Lactate of Donor Heart

OCS Parameters/Session	
Baseline Donor Arterial Lactate	ND
Pre-Instrumentation Lactate on OCS	1.99 mmol/L
Initial Arterial Lactate on OCS Initial Venous Lactate on OCS	3.16 mmol/L 3.23 mmol/L
Final Arterial Lactate on OCS Final Venous Lactate on OCS	2.56 mmol/L 2.38 mmol/L
Total OCS Perfusion Duration (time)	294 min
Donor Heart Out of Body Time	425 min

Recipient Outcome: The recipient underwent heart transplantation on (b)(6). During surgery, the patient was coagulopathic and the sternum was left open due to bleeding. IABP was inserted intraoperatively due to RV dysfunction. On POD#1 the patient was diagnosed with Severe LV PGD. Echo on POD#1 showed EF 25%, hypokinetic LV and RV with moderate dilatation. The patient's post- transplant course was complicated by the following events:

- Multiple organ failure secondary to biventricular dysfunction on POD#1.

- On (b) (4) ECMO was decannulated due to RVAD implantation and improved LV function.
- On (b) (4), the subject coded on the floor and emergent ECMO was deployed.
- On (b) (4), subject was found to have hemorrhagic shock with large volume of blood in right chest with ongoing biventricular dysfunction. Care was withdrawn and subject was declared dead. This event was adjudicated to be an anticipated heart graft-related event (Severe PGD-LV and Severe PGD-RV), possibly related to preservation, and resulting in death.

The patient was never discharged from the hospital following transplantation.

Recipient Death: The patient expired on (b) (4) (12 days post-transplantation) in the hospital. The site-reported cause of death was "Multiple Organ Failure." The adjudicated cause of death was Multiple Organ Failure Secondary to Primary Graft Dysfunction.

13.3. Patient ID (b)(6)

Donor History (UNOS ID (b)(6)): A 44-year-old male donor that died due to anoxia with 15 minutes of cardiac arrest. The donor was noted to be CMV+ with a history of drug use within 6 months of death. The donor angiogram and echocardiogram did not display any abnormal findings.

Recipient History: A 65-year-old, status 1A male diagnosed with non-ischemic cardiomyopathy with an LVAD placed on (b) (4). The recipient had history of advanced liver cirrhosis. Operative notes indicated recurrent hospital readmissions post-VAD for heart failure and ventricular tachycardia.

Retrieval and OCS Perfusion: The donor heart was accepted into the trial because of an expected total cross-clamp time ≥ 4 hours. The donor heart was surgically retrieved on (b) (4) and perfused on the OCS Heart System. Perfusion trends of the donor heart were not stable throughout preservation on the OCS Heart System, and Lactate trend was rising throughout the OCS preservation session (see Table 49); however, the clinical decision was to proceed with the transplant based on clinical judgment.

Table 49: OCS Perfusion Parameters and Lactate of Donor Heart

OCS Parameters/Session	
Baseline Donor Arterial Lactate	0.64 mmol/L
Pre-Instrumentation Lactate on OCS	0.61 mmol/L
Initial Arterial Lactate on OCS Initial Venous Lactate on OCS	1.43 mmol/L 1.53 mmol/L
Final Arterial Lactate on OCS Final Venous Lactate on OCS	4.73 mmol/L 4.86 mmol/L
Total OCS Perfusion Duration (time)	212 min

OCS Parameters/Session	
Donor Heart Out of Body Time	279 min

Recipient Outcome: The recipient underwent heart transplantation on (b) (4). The subject was not diagnosed with PGD in the first 24 hours post-transplant. The patient's post-transplant course was complicated by the following SAEs:

- On POD#2 Liver failure related to pre-existing liver cirrhosis with an onset date of (b) (4), initially requiring dialysis catheter insertion. This event was adjudicated to be an anticipated, unrelated to preservation, and resulting in death.
- Respiratory distress with an onset date of (b) (4), requiring tracheostomy. This event was adjudicated to be an anticipated, unlikely related to preservation, and ongoing at the time of death.
- Fungemic sepsis with an onset date of (b) (4), requiring antibiotics. This event was adjudicated to be an anticipated, unrelated to preservation, and ongoing at the time of death.

The patient was never discharged from the hospital following transplantation.

Recipient Death: The patient expired on (b) (4) (29 days post-transplantation) in the hospital. The site-reported cause of death was "Multiple Organ Failure." The adjudicated cause of death was Multiple Organ Failure Secondary to Pre-existing Liver Cirrhosis.

13.4. Patient ID (b)(6)

Donor History (UNOS ID (b)(6)): A 35-year-old female donor that died due to anoxia. The donor was noted to be CMV+ with a history of drug use within 6 months of death. The donor echocardiogram did not display any abnormal findings other than a trivial pericardial effusion.

Recipient History: A 45-year-old, status 1B female diagnosed with restrictive cardiomyopathy. The patient was noted to have high Pulmonary Vascular Resistance (PVR) in the medical record.

Retrieval and OCS Perfusion: The donor heart was accepted into the trial because of an expected total cross-clamp time ≥ 2 hours with a reported down time ≥ 20 minutes with stable hemodynamics at time of assessment. The donor heart was surgically retrieved on (b) (4) and perfused on the OCS Heart System. Perfusion trends of the donor heart were not stable throughout preservation on the OCS Heart System, as the lactate trend was rising throughout the OCS preservation session (see Table 50); however, the clinical decision was to proceed with the transplant based on clinical judgment.

Table 50: OCS Perfusion Parameters and Lactate of Donor Heart

OCS Parameters/Session	
Baseline Donor Arterial Lactate	1.31 mmol/L
Pre-Instrumentation Lactate on OCS	ND
Initial Arterial Lactate on OCS	1.11 mmol/L

OCS Parameters/Session	
Initial Venous Lactate on OCS	ND
Final Arterial Lactate on OCS Final Venous Lactate on OCS	4.59 mmol/L 4.54 mmol/L
Total OCS Perfusion Duration (time)	278 min
Donor Heart Out of Body Time	406 min

Recipient Outcome: The recipient underwent heart transplantation on (b) (4) Operative notes indicated that because of chronically inflamed tissues surgeon elected not to perform bicaval anastomosis as the SVC looked fragile. In addition, the notes indicated that the donor heart was "very big" compared to the "tiny pericardial cavity" and reiterated several references to size mismatch.

The patient's post-transplant course was complicated by the following SAE:

- Severe RV dysfunction leading to biventricular failure at POD#1, leading to RVAD placement. RVAD was removed on POD# 11. RV failure leading to biventricular failure with an onset date of (b) (4), initially requiring intra-aortic balloon pump, RVAD placement, and nitric oxide therapy. This event was adjudicated to be anticipated, possibly related to preservation, heart graft-related (PGD-RV) and resulting in death.

The patient was never discharged from the hospital following transplantation.

Recipient Death: The patient expired on (b) (4) (18 days post-transplantation) in the hospital. The site-reported cause of death was "Primary Graft Dysfunction." The adjudicated cause of death was Primary Graft Dysfunction.

13.5. Patient ID (b)(6)

Donor History (UNOS ID (b)(6)): A 52-year-old male donor that died due to head trauma. The donor was noted to be CMV+ with history of drug use, but not continuing within 6 months of death. The donor angiogram noted mid 30% stenosis of the Circumflex. The donor echocardiogram was suggestive of impaired LV relaxation, mildly dilated IVC and mild aortic valve incompetence.

Recipient History: A 58-year-old, status 1A male diagnosed with ischemic cardiomyopathy, with AICD and requiring an IABP to be placed on (b) (4). The recipient was noted to have a history of type II diabetes.

Retrieval and OCS Perfusion: The donor heart was accepted into the trial because of an expected total cross-clamp time ≥ 2 hours with a donor angiogram with luminal irregularities without significant coronary artery disease. The donor heart was surgically retrieved on (b) (4) and perfused on the OCS Heart System. Perfusion trends of the donor heart were stable throughout preservation on the OCS Heart System and met implantation criteria per protocol definition and clinical judgment (as seen in Table 51).

Table 51: OCS Perfusion Parameters and Lactate of Donor Heart

OCS Parameters/Session	
Baseline Donor Arterial Lactate	1.42 mmol/L
Pre-Instrumentation Lactate on OCS	1.06 mmol/L
Initial Arterial Lactate on OCS Initial Venous Lactate on OCS	1.74 mmol/L 1.83 mmol/L
Final Arterial Lactate on OCS Final Venous Lactate on OCS	2.24 mmol/L 2.03 mmol/L
Total OCS Perfusion Duration (time)	230 min
Donor Heart Out of Body Time	326 min

Recipient Outcome: The recipient underwent heart transplantation on (b) (4). The subject was not diagnosed with PGD in the first 24 hours post-transplant and POD#1 Echo showed EF 55%. The patient's post-transplant course was complicated by the following SAEs:

- Arrhythmia with onset on (b) (4) and requiring medication. This event was adjudicated to be anticipated, unlikely related to preservation, and resolving without sequelae.
- Acute rejection with onset on (b) (4) and requiring medication. This event was adjudicated to be anticipated, unlikely related to preservation, and resolving without sequelae.
- Acute respiratory distress, with an onset date of (b) (4), initially requiring IV vancomycin and Zosyn. The subject returned to the ICU on (b) (4) on high flow oxygen and Bipap, followed by the subject being re-intubated on (b) (4). Tracheostomy was placed on (b) (4) and subject was placed on VV ECMO for respiratory support on (b) (4). Pulmonary consultation speculated possible undiagnosed parenchymal lung disease leading to post-op ARDS. It was determined that the subject would not make a recovery from impaired lung function, and care was withdrawn on (b) (4). This event was adjudicated to be anticipated, unrelated to preservation, and resulting in death.

The patient was never discharged from the hospital.

Recipient Death: The patient expired on (b) (4) (80 days post-transplantation). The site-reported cause of death was "Acute Respiratory Distress Disease." The adjudicated cause of death was Acute Respiratory Distress Disease.

13.6. Patient ID (b)(6)

Donor History (UNOS ID (b)(6)): A 23-year-old male donor that died due to head trauma.

Recipient History: A 52-year-old, status 1A male diagnosed with non-ischemic cardiomyopathy, with an LVAD placed on (b) (4). The recipient was noted to have a history of type II diabetes.

Retrieval and OCS Perfusion: The donor heart was accepted into the trial because of an expected total cross-clamp time > 4 hours. The donor heart was surgically retrieved on (b) (4) and perfused on the OCS Heart System. Perfusion trends of the donor heart were stable throughout preservation on the OCS Heart System and met implantation criteria per protocol definition and clinical judgment (as seen in Table 52).

Table 52: OCS Perfusion Parameters and Lactate of Donor Heart

OCS Parameters/Session	
Baseline Donor Arterial Lactate	4.06 mmol/L
Pre-Instrumentation Lactate on OCS	2.78 mmol/L
Initial Arterial Lactate on OCS Initial Venous Lactate on OCS	3.44 mmol/L 3.52 mmol/L
Final Arterial Lactate on OCS Final Venous Lactate on OCS	3.67 mmol/L 3.59 mmol/L
Total OCS Perfusion Duration (time)	184 min
Donor Heart Out of Body Time	277 min

Recipient Outcome: The recipient underwent heart transplantation on (b) (4). The subject was not diagnosed with PGD in the first 24 hours post-transplant. Intraoperative Echo showed good biventricular function after removal of CPB. The patient's post-transplant course was complicated by the following SAEs:

- Intraoperatively POD#0: Patient was severely coagulopathic, vasoplegic and hypoxic post-CPB. Interventions were undertaken and biventricular function remained good coming out of OR.
- POD#1: Shock liver.
- POD#2: Renal insufficiency.
- POD#12: Respiratory failure.
- Multiple Organ Failure with onset on (b) (4). This event was adjudicated to be anticipated, unrelated to preservation, and resulting in death.

The patient was never discharged from the hospital.

Recipient Death: The patient expired on (b) (4) (49 days post-transplantation). The site-reported cause of death was "Multi-Organ Failure." The adjudicated cause of death was Multi-Organ Failure.

13.7. Patient ID(b)(6)

Donor History (UNOS ID(b)(6)): A 39-year-old female donor that died due to head trauma. The donor was noted to be CMV+ with a history of drug use within 6 months of death. The donor angiogram and echocardiogram did not display any abnormal findings.

Recipient History: A 63-year-old, status 1A female diagnosed with ischemic cardiomyopathy with an LVAD placed on(b)(6) . The recipient was noted to have a history of type II diabetes. The patient had a significant pre-transplant medical history which included multiple ICU hospitalization due to respiratory compromise, renal compromise and delirium.

Retrieval and OCS Perfusion: The donor heart was accepted into the trial because of an expected total cross-clamp time ≥ 2 hours with a social history of alcoholism with good cardiac function at time of donor assessment. The donor heart was surgically retrieved on(b)(6) and perfused on the OCS Heart System. Perfusion trends of the donor heart were stable throughout preservation on the OCS Heart System and met implantation criteria per protocol definition and clinical judgment (as seen in Table 53).

Table 53: OCS Perfusion Parameters and Lactate of Donor Heart

OCS Parameters/Session	
Baseline Donor Arterial Lactate	0.99 mmol/L
Pre-Instrumentation Lactate on OCS	0.64 mmol/L
Initial Arterial Lactate on OCS Initial Venous Lactate on OCS	1.69 mmol/L 1.81 mmol/L
Final Arterial Lactate on OCS Final Venous Lactate on OCS	2.71 mmol/L 2.69 mmol/L
Total OCS Perfusion Duration (time)	282 min
Donor Heart Out of Body Time	369 min

Recipient Outcome: The recipient underwent heart transplantation on(b)(6) . The operative report stated that intraoperative VA ECMO was initiated and the chest was left open due to RV failure/dysfunction. The patient's post-transplant course was complicated by the following SAEs:

- POD#0: RV failure secondary to surgical pulmonary artery stenosis with an onset date of(b)(6) , requiring VA ECMO placement intraoperatively and the patient's chest was left open with the ECMO being discontinued on(b)(6) . The subject was also treated with inhaled nitric oxide.
- Reoperation – Pulmonary Artery Anastomosis Revision/Surgical Complication with onset date of(b)(6) . This event was adjudicated to be anticipated, unlikely related to preservation, and resolving without sequelae.
- POD#5: ECMO was discontinued.
- Other complications included prolonged ventilation, renal insufficiency, endocarditis.

The patient remained in the ICU for 112 days.

Recipient Death: The patient expired on November 4, 2016 (138 days post-transplantation). Autopsy notes extensive pericardial adhesions, mitral valve endocarditis, marked pleural adhesions, abdominal atherosclerosis and diverticular disease. The site-reported cause of death was "Unknown, Possible Complication of Endocarditis." The adjudicated cause of death was Multi-Organ Failure and Endocarditis.

13.8. Patient ID (b)(6)

Donor History (UNOS ID (b)(6)): A 35-year-old male donor that died due to head trauma. The donor was noted to be CMV+. The donor echocardiogram noted an ejection fraction of 50%, mild LV wall motion abnormalities, mild tricuspid regurgitation and aortic valve sclerosis without stenosis.

Recipient History: An 18-year-old, status 1A female diagnosed with severe non-ischemic cardiomyopathy, cardiogenic shock with an LVAD placed on (b) (4) .

Retrieval and OCS Perfusion: The donor heart was accepted into the trial because of an expected total cross-clamp time ≥ 2 hours with a left heart ejection fraction ≥ 40% and ≤ 50%. The donor heart was surgically retrieved on (b) (4) and perfused on the OCS Heart System. Perfusion trends of the donor heart were stable throughout preservation on the OCS Heart System and met implantation criteria per protocol definition and clinical judgment (as seen in Table 54).

Table 54: OCS Perfusion Parameters and Lactate of Donor Heart

OCS Parameters/Session	
Baseline Donor Arterial Lactate	1.67 mmol/L
Pre-Instrumentation Lactate on OCS	1.13 mmol/L
Initial Arterial Lactate on OCS Initial Venous Lactate on OCS	1.72 mmol/L 1.77 mmol/L
Final Arterial Lactate on OCS Final Venous Lactate on OCS Final Arterial pH	1.86 mmol/L 1.82 mmol/L 7.467
Total OCS Perfusion Duration (time)	244 min
Donor Heart Out of Body Time	334 min

Recipient Outcome: The recipient underwent heart transplantation on (b) (4) . The subject was not diagnosed with PGD in the first 24 hours post-transplant. The patient's post-transplant course was complicated by the following SAEs:

- Right subclavian DVT with onset on (b) (4) and requiring medication. This event was adjudicated to be anticipated, unrelated to preservation, and resolving without sequelae.

- The patient suffered cardiac arrest at home with onset date of (b) (4) that was determined to be secondary to massive bilateral pulmonary emboli and several lower extremity thrombi. This event was adjudicated to be unanticipated, unrelated to preservation, and resolved with sequelae.
- Massive PE with RV dysfunction with onset date of (b) (4)
- Severe hypoxic ischemic encephalopathy with onset on (b) (4). MRI showed severe hypoxic ischemic encephalopathy and care was terminated and recipient died.

Recipient Death: The patient expired on (b) (4) (119 days post-transplantation). The site-reported cause of death was "Severe Hypoxic Ischemic Encephalopathy." The adjudicated cause of death was Severe Hypoxic Ischemic Encephalopathy Secondary to Pulmonary Embolism.

13.9. Patient ID (b)(6)

Donor History (UNOS ID (b)(6)): A 23-year-old female donor who died due to acute respiratory failure with witnessed cardiac arrest lasting for approximately 20 minutes and requiring CPR. The donor echocardiogram did not note any abnormalities. The donor was noted to be CMV+.

Recipient History: A 23-year-old, status 1A male diagnosed with non-ischemic cardiomyopathy, with an LVAD placed on (b) (4). Patient had a severe driveline infection secondary to multi-drug resistant pseudomonas infection.

Retrieval and OCS Perfusion: The donor heart was accepted into the trial because of an expected total cross-clamp time ≥ 2 hours with a reported down time ≥ 20 minutes with stable hemodynamics at time of assessment. The donor heart was surgically retrieved on (b) (4) and perfused on the OCS Heart System. Perfusion trends of the donor heart were stable throughout preservation on the OCS Heart System and met implantation criteria per protocol definition and clinical judgment (as seen in Table 55).

Table 55: OCS Perfusion Parameters and Lactate of Donor Heart

OCS Parameters/Session	
Baseline Donor Arterial Lactate	0.99 mmol/L
Pre-Instrumentation Lactate on OCS	0.92 mmol/L
Initial Arterial Lactate on OCS Initial Venous Lactate on OCS	1.35 mmol/L 1.54 mmol/L
Final Arterial Lactate on OCS Final Venous Lactate on OCS	2.85 mmol/L 2.45 mmol/L
Total OCS Perfusion Duration (time)	102 min
Donor Heart Out of Body Time	173 min

Recipient Outcome: The recipient underwent heart transplantation on (b) (4). The subject was not diagnosed with PGD in the first 24 hours post-transplant. The patient's post-transplant course was complicated by the following SAE:

- POD# 2: Primary graft dysfunction initially requiring increasing pressor requirements and CVVH due to minimal urine output. Patient developed cardiogenic shock with severe biventricular dysfunction including LVEF of < 10-15%. IABP and ECMO were placed on POD# 2.
- On (b) (4), Patient developed respiratory distress and was re-intubated. On (b) (4), ECMO was explanted followed by implantation of an LVAD. The subject returned to the OR on (b) (4) for mediastinal exploration, IABP re-placement. A subsequent echocardiogram revealed an EF of 32%, following by LVAD removal on (b) (4) and the IABP was removed on (b) (4). The patient developed fevers on (b) (4) (multi-focal pneumonia), and on (b) (4), the patient began to have notable seizures (multifocal sub-clinical seizures). On (b) (4), the patient was transferred back to Israel, where he subsequently expired. The primary graft dysfunction and multi-organ failure was adjudicated to be anticipated, heart graft-related (severe PGD-LV), possibly related to preservation, and resulting in death.

The patient was discharged from the hospital on (b) (4).

Recipient Death: The patient expired on (b) (4) (64 days post-transplantation). The site-reported cause of death was "Multi-Organ Failure." The adjudicated cause of death was Multi-Organ Failure Secondary to Primary Graft Dysfunction.

13.10. Patient ID (b)(6)

Donor History (UNOS ID (b)(6)): A 56-year-old male donor who died due to anoxia with cardiac arrest lasting for approximately 60 minutes. The donor was noted to be CMV+. The donor angiogram noted mild luminal irregularities of the LAD (20% proximal stenosis) and RCA (20% proximal stenosis).

Recipient History: A 65-year-old, status 1B male diagnosed with ischemic cardiomyopathy, with an LVAD placed on (b) (4). The recipient was noted to have a history of type II diabetes.

Retrieval and OCS Perfusion: The donor heart was accepted into the trial because of an expected total cross-clamp time ≥ 2 hours with the following risk factors: donor age > 55 years, reported down time of ≥ 20 minutes with stable hemodynamics at time of final assessment, and a donor angiogram with luminal irregularities with no significant coronary artery disease. The donor heart was surgically retrieved on (b) (4) and perfused on the OCS Heart System. Perfusion trends of the donor heart were stable throughout preservation on the OCS Heart System, and met implantation criteria per protocol definition and clinical judgment (as seen in Table 56).

Table 56: OCS Perfusion Parameters and Lactate of Donor Heart

OCS Parameters/Session	
Baseline Donor Arterial Lactate	1.55
Pre-Instrumentation Lactate on OCS	0.88 mmol/L
Initial Arterial Lactate on OCS Initial Venous Lactate on OCS	1.23 mmol/L 1.36
Final Arterial Lactate on OCS Final Venous Lactate on OCS	2.06 mmol/L 2.04 mmol/L
Total OCS Perfusion Duration (time)	252 min
Donor Heart Out of Body Time	324 min

Recipient Outcome: The recipient underwent heart transplantation on (b) (4). The intraoperative course was complicated by left atrial suture line tear after administration of Protamine and emergency reinstatement of CPB to repair the left atrial tear. The subject was not diagnosed with PGD in the first 24 hours post-transplant. The patient's post-transplant course was complicated by the following SAEs:

- Left atrium tear due to a surgical complication, with an onset date of (b) (4). Protamine was administered to reverse the anticoagulation and all cannulae for bypass were removed. After Protamine was slowly administered, there continued to be bleeding which originated from the left atrium near the base of the left atrial appendage. There appeared to be a significant tear in the left atrium, which extended up near the left superior pulmonary vein, which the surgeon did not feel that this could be adequately repaired off bypass. Subject was then re-heparinized over 300 units per kg of sodium heparin. Aortic cannula was re-inserted into the mid ascending aorta and a purse-string suture was placed in the right atrial appendage and a two-stage cannula was inserted, with CPB reinitiated. The tear was then repaired with CPB weaned. Protamine was administered reversing anticoagulation. This event was adjudicated to be anticipated, unrelated to preservation, and resolving without sequelae.
- Stroke, with an onset date of (b) (4). Stroke team was activated due to concern for patient not moving left arm and leg after weaning sedation. On (b) (4) the patient was able to follow intermittent commands. The subject was given Keppra, Ativan, and Valproate. The subject experienced some anxiety and agitation on (b) (4). A tracheostomy was performed on (b) (4). The subject was transferred out of the ICU on (b) (4), answering questions appropriately, but still getting nutrition via feeding tube. This event was adjudicated to be anticipated, unrelated to preservation, and resolving with sequelae.
- PEA arrest, with an onset date of (b) (4), requiring 5 rounds ACLS with one shock, left sided chest tube, blood transfusions, and pressor support. This event was adjudicated to be anticipated, unrelated to preservation, and resolving without sequelae.

The patient was discharged from the hospital on (b) (4)

Recipient Death: The patient expired on (b) (4) (314 days post-transplantation). The site-reported cause of death was "Sepsis, Pneumonia." The adjudicated cause of death was Sepsis, Pneumonia.

13.11. Patient ID (b)(6)

Donor History (UNOS ID (b)(6)): A 33-year-old female donor who died due to anoxia with cardiac arrest lasting for approximately 55 minutes. The donor was noted to be CMV+. The donor echocardiogram noted an ejection fraction of 40%, severe LV wall motion abnormalities, and mild tricuspid regurgitation.

Recipient History: A 44-year-old, status 1A female diagnosed with amyloidosis.

Retrieval and OCS Perfusion: The donor heart was accepted into the trial because of an expected total cross-clamp time ≥ 2 hours with a reported down time of ≥ 20 minutes with stable hemodynamics at time of final assessment. The donor heart was surgically retrieved on (b) (4) and perfused on the OCS Heart System. Perfusion trends of the donor heart were stable throughout preservation on the OCS Heart System and met implantation criteria per protocol definition and clinical judgment (as seen in Table 57).

Table 57: OCS Perfusion Parameters and Lactate of Donor Heart

OCS Parameters/Session	
Baseline Donor Arterial Lactate	ND
Pre-Instrumentation Lactate on OCS	0.69 mmol/L
Initial Arterial Lactate on OCS Initial Venous Lactate on OCS	1.71 mmol/L 1.81 mmol/L
Final Arterial Lactate on OCS Final Venous Lactate on OCS	2.06 mmol/L 2.02 mmol/L
Total OCS Perfusion Duration (time)	202 min
Donor Heart Out of Body Time	304 min

Recipient Outcome: The recipient underwent heart transplantation on (b) (4). The subject was not diagnosed with PGD in the first 24 hours post-transplant. The patient's post-transplant course was complicated by the following AEs:

- Acute Kidney Injury, with an onset date of (b) (4) initially requiring CRRT and vasopressin to maintain a mean arterial pressure > 80 for renal perfusion. The subject required continuous venovenous hemodiafiltration, with the last hemodialysis completed on (b) (4). This event was adjudicated to be anticipated, unrelated to preservation, and resolving without sequelae.

- Acute rejection, with an onset date of (b) (4), with a biopsy grade of 2R/3A and requiring IV solumedrol. This event was adjudicated to be anticipated, unrelated to preservation, and resolving without sequelae.
- The patient was discharged from the hospital on (b) (4). The patient was readmitted to hospital 5 months after initial discharge due to presence of multiple myeloma and AL Amyloidosis.

Recipient Death: The patient expired on (b) (4) (212 days post-transplantation). The site-reported cause of death was "Re-occurring amyloidosis with refractory GI Bleed." The adjudicated cause of death was Re-Occurring Amyloidosis with Refractory GI Bleed.

13.12. Patient ID (b)(6)

Donor History (UNOS ID (b)(6)): A 56-year-old female donor who died due to cerebrovascular hemorrhage with witnessed cardiac arrest lasting for 2 minutes and requiring CPR. The donor echocardiogram did not note any abnormalities. The donor had a history of hypertension and was known to have heavy alcohol use and a history of cocaine use.

Recipient History: A 66-year-old, status 1A female diagnosed with ischemic cardiomyopathy, with an LVAD placed on (b) (4). Recipient also supported with an AICD.

Retrieval and OCS Perfusion: The donor heart was accepted into the trial because of an expected total cross-clamp time ≥ 2 hours with an age ≥ 55 years and social history of alcoholism with good cardiac function at the time of donor assessment. The donor heart was surgically retrieved on (b) (4) and perfused on the OCS Heart System. Perfusion trends of the donor heart were not stable throughout preservation on the OCS Heart System, and Lactate trend was rising throughout the OCS preservation session (see Table 58); however, the clinical decision was to proceed with the transplant based on clinical judgment.

Table 58: OCS Perfusion Parameters and Lactate of Donor Heart

OCS Parameters/Session	
Baseline Donor Arterial Lactate	0.44 mmol/L
Pre-Instrumentation Lactate on OCS	0.64 mmol/L
Initial Arterial Lactate on OCS Initial Venous Lactate on OCS	1.63mmol/L 1.79 mmol/L
Final Arterial Lactate on OCS Final Venous Lactate on OCS	4.18 mmol/L 4.24 mmol/L
Total OCS Perfusion Duration (time)	278 min
Donor Heart Out of Body Time	364 min

Recipient Outcome: The recipient underwent heart transplantation on (b) (4). The subject was not diagnosed with PGD in the first 24 hours post-transplant. The patient's post-transplant course was complicated by the following SAE:

- POD# 2: Right frontal lobe subacute infarction by CT scan. This event was adjudicated to be anticipated, unrelated to preservation, and resolving with sequelae.
- The recipient was re-admitted to the hospital on (b) (4) due to severe antibody-mediated rejection along with acute cellular rejection. Right heart catheterization and endomyocardial biopsy performed on (b) (4) due to mild acute post-operative rejection. Findings included normal right-sided pressures, normal PVRI, increased PCW and extremely low cardiac output. Biopsy demonstrated grade 1R acute cellular rejection.
- Recipient experienced cardiogenic shock with a hospital course complicated by seizures, respiratory failure requiring tracheostomy, bilateral radial artery thrombosis, as well as right subclavian and bilateral internal jugular DVTs, AKI/ESRD requiring HD, persistent thrombocytopenia, stage IV sacral decubitis, CMV reactivation/viremia, invasive pulmonary aspergillosis, as well as possible mucormycosis and multiple septic episodes from polymicrobrial blood-stream infections and hospital-acquired pneumonia. The recipient eventually developed shock (likely multi-factorial – including septic) and died on (b) (4)

Recipient Death: The patient expired on (b) (4) (205 days post-transplantation). The site-reported cause of death was "Septic shock." The adjudicated cause of death was Multifactorial septic shock following acute rejection.

13.13. Patient ID (b)(6)

Donor History (UNOS ID (b)(6)): 24-year old male, who died from head trauma on (b) (4). Donor was involved in MVA and had evidence of chest injury. Donor is noted to be an active drug user. Donor eligibility was expected cross-clamp time of ≥ 4 hours.

Recipient History: A 37-year old male, heart allocation status 4, indication for heart transplant was ischemic cardiomyopathy. Patient was not any cardiac support prior to transplant. Recipient's prior history includes Hodgkin's Lymphoma treated with radiation and subsequently radiation induced coronary sclerosis. He also had two prior CABG procedures, in (b) (4) and (b).

Retrieval and OCS Perfusion: The donor heart was surgically retrieved on (b) (4) and perfused on the OCS Heart System. After a 2-hour period of stabilization, perfusion trends of the donor heart were stable throughout the balance of preservation on the OCS Heart System and met implantation criteria per protocol definition and clinical judgment (Table 59).

Table 59: OCS Perfusion Parameters and Lactate of Donor Heart

OCS Parameters/Session	
Baseline Donor Arterial Lactate	Not Done
Pre-Instrumentation Lactate on OCS (mmol/L)	1.94
Initial Arterial Lactate on OCS (mmol/L)	2.42

OCS Parameters/Session	
Initial Venous Lactate on OCS (mmol/L)	2.45
Organ Acceptance lactate on OCS (Arterial) (mmol/L)	Not Available
Final Arterial Lactate on OCS (mmol/L) Final Venous Lactate on OCS (mmol/L)	4.04 4.15
Total OCS Perfusion Duration Time (min)	288
Donor Heart Out of Body Time (min)	394

Recipient Outcome: The recipient underwent heart transplantation on (b) (4). No surgical complications during surgery were reported. Mechanic circulatory support was not used in early post-transplant period. No PGD was reported in the first 24 hours post-transplant. Patient did not experience any adverse events following the transplant procedure. Patient was discharged 11 days post-transplant, on (b) (4).

Late post-transplant course was complicated by two hospital readmissions, first readmission was for sternal osteomyelitis between (b) (4) and (b) (4). Patient was admitted with fever, upon examination sternal non union was found and surgically repaired, cultures confirmed MRSA and antibiotics started (stop date (b) (4)). Of note, patient had a pre-existing sternal wound osteomyelitis, prior to heart transplant.

Second readmission was for surgical intervention for MRSA infection/Pectoral flap between (b) (4) and (b) (4). During this readmission pectoral flap was performed. Cultures taken during the surgery once again grew MRSA, vancomycin started (stop date (b) (4)).

On (b) (4) patient underwent sternotomy revision and required circulatory arrest for pseudoaneurysm repair. Sternal closure was planned to be finalized on (b) (4) but upon ICU admission post sternotomy revision, patient started to have seizure-like activity, head CT revealed cerebral edema and bilateral watershed infarcts. His neurological status worsened; no procedures were recommended due to diffuse nature of ischemia. Family was consulted and they decided to withdraw care due to poor prognosis.

Recipient Death: Patient died 227 days post-transplant, on (b) (4). Cause of death is reported as a non-recoverable cerebrovascular event.

14. (b)(4)

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