SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Portable *Ex Vivo* Organ Perfusion System for Donor Hearts
Device Trade Name:	Organ Care System (OCS™) Heart System
Device Procode:	QIK
Applicant Name and Address:	TransMedics, Inc. 200 Minuteman Road, Suite 302 Andover, MA 01810
Date of Panel Recommendation:	N/A
Premarket Approval Application (PMA) Number:	P180051/S001
Date of FDA Notice of Approval:	April 27, 2022
Breakthrough Device:	Granted breakthrough device status for the indication of donation-after-circulatory-death (DCD) hearts preservation on May 11, 2018, because the device can provide for more effective treatment of an irreversibly debilitating disease; as well represents a breakthrough technology, has no approved or cleared alternatives, and is in the best interest of patients.

The original PMA of the TransMedics OCS Heart System, P180051, was approved on September 3, 2021, and was indicated for the preservation of donation-after-brain-death (DBD) hearts deemed unsuitable for procurement and transplantation at initial evaluation due to limitations of prolonged cold static cardioplegic preservation (e.g., > 4 hours of cross-clamp time). The SSED to support the indication is available on the CDRH website (https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180051B.pdf) and is incorporated by reference herein. The current supplement was submitted to expand the indication for the OCS Heart System to include the preservation of DCD hearts.

II. INDICATIONS FOR USE

The TransMedics Organ Care System (OCS) Heart is indicated for the preservation of donation-after-brain-death (DBD) hearts initially deemed unsuitable for procurement and transplantation at initial evaluation due to limitations of prolonged cold static cardioplegic

preservation (e.g., > 4 hours of cross-clamp time). The OCS Heart System is also indicated for the *ex vivo* reanimation, functional monitoring, and beating-heart preservation of donation-after-circulatory-death (DCD) hearts.

III. CONTRAINDICATIONS

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

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

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

Figure 1: Components of the OCS Heart System

- **Heart Console:**

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

- **HPS:**

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

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

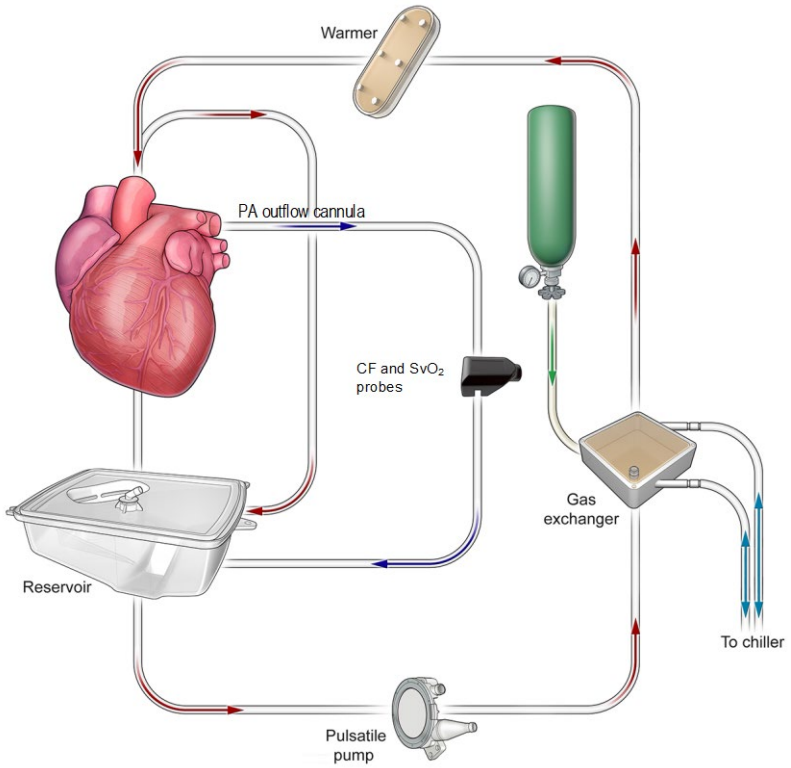
- **OCS Heart Solution Set:**

  The OCS Heart Solution Set consists of two proprietary heart preservation solutions: the OCS Priming Solution and the OCS Maintenance Solution. Additives are required at the time of use that are supplied and added by the user. The OCS Heart Solution Set is not intended to be administered directly to the donor or the recipient.

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

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

Figure 2: Schematic of the OCS Heart System Circuit



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are currently no other alternatives for the preservation of DCD hearts for transplantation. For patients on the donor heart waitlist, the alternative to receiving a DCD heart preserved with the OCS Heart System is to receive a DBD heart preserved with cold static preservation or with the OCS Heart System. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

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

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

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

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

IX. SUMMARY OF NONCLINICAL STUDIES

A summary of previously reported preclinical studies can be found in the SSED for the original PMA. No additional preclinical study was performed for the current application.

X. SUMMARY OF PRIMARY CLINICAL STUDY

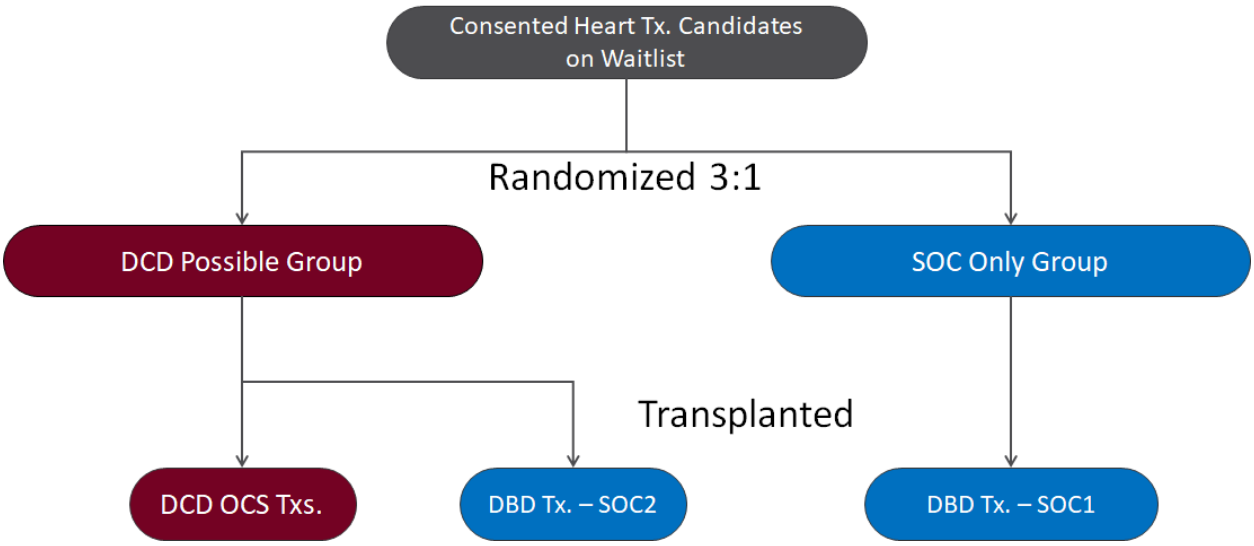
The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the OCS Heart System for the preservation of DCD hearts under IDE G180272 (entitled the "DCD Heart Trial"). The data from this study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The DCD Heart Trial was a prospective, two-arm, multicenter study, as illustrated in Figure 3. Eligible patients were randomized (3:1) into two groups: DCD Heart Possible and Standard-of-Care (SOC) Heart Only (SOC1). Patients randomized to the DCD Heart Possible group could receive a DCD heart preserved with the OCS Heart System or a DBD heart preserved with cold static preservation, whichever is available first. In contrast, patients randomized to the SOC1 group could only receive a DBD heart preserved with cold static preservation. In the DCD Heart Possible group, patients who received a DBD heart formed a

second SOC heart group (SOC2). The trial compared the outcomes of donor heart recipients who received a DCD heart with those of donor heart recipients who received a DBD heart (SOC1 + SOC2).

Figure 3: DCD Heart Trial Design Overview



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

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the DCD Heart Trial was limited to donor hearts and transplant recipient patients that met the following inclusion criteria:

   All recipients:

   - Primary heart transplant candidates;
   - Age ≥ 18 years old; and
   - Signed written informed consent document, authorization to use and disclose protected health information, and consent to use of data.

   DCD heart prior to preservation:

   - Maastricht Category III DCD donor, defined as expected death after the withdrawal of life-supportive therapy (WLST);
   - Donor age: 18-49 years old (inclusive); and

- Warm ischemic time (WIT) ≤ 30 minutes, with WIT being defined as: time from when mean systolic blood pressure (SBP) is < 50 mmHg or peripheral saturation < 70% to aortic cross-clamp and administration of cold cardioplegia in the donor.

DCD heart post preservation:

- Stable or downward trending lactate after initial adjustments of the OCS Heart System perfusion parameters to achieve adequate perfusion to the donor heart;
- Stability of OCS Heart System perfusion parameters within range:
  - aortic pressure (AOP): 40-100 mmHg; and
- Transplanting surgeon and/or heart failure cardiologist must clinically accept the donor heart for transplant.

DBD heart prior to preservation:

- Accepted per standard of care at each institution.

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

DCD heart:

- Previous cardiac surgery; or
- Known coronary artery disease; or
- Cardiogenic shock or myocardial infarction; or
- Sustained terminal EF of ≤ 50%; or
- Significant valve disease except for competent bicuspid aortic valve.

DBD heart:

- Rejected per standard of care at each institution.

Recipient:

- Prior solid organ or bone marrow transplant; or
- Chronic use of hemodialysis or diagnosis of chronic renal insufficiency;
- Multi-organ transplant; or
- Investigator unwilling to randomize the patients.

2. Follow-up Schedule

Follow-up time points included day of transplant, immediately post-transplant, 24 hours, 72 hours, initial hospital discharge, 30 days, 6 months, and 1 year, and annually thereafter to 5 years post procedure. Pre- and post-implant assessments included medical and cardiac history, need for mechanical circulatory or respiratory support, heart graft-related

adverse events and serious adverse events, and patient/graft survival. Heart graft-related serious adverse events (HGRSAEs) and serious adverse events (SAEs) were recorded through the 30-day visit.

3. Clinical Endpoints

The primary endpoint was survival at 6 months post-transplant. The primary hypothesis was as follows:

$$H_0: p_{SOC} - p_{DCD} \geq 0.20$$
$$H_1: p_{SOC} - p_{DCD} < 0.20$$

where p_{SOC} and p_{DCD} represent the true survival proportions at 6 months for the SOC and DCD heart transplant patients, respectively, and 0.20 is the non-inferiority margin. The primary analysis was adjusted for known mortality risk factors of the donor heart (including, initially, donor age ≥ 55 years, ischemic time ≥ 4 hours, and female donor heart to male recipient mismatch) and the recipient (including, initially, age ≥ 65 years, mechanical circulatory support (MCS) pre-transplant, and mechanical ventilation at time of transplant), using a linear probability model, with factors being dropped until the model converged. The final model included two adjusted factors: ischemic time ≥ 4 hours and MCS pre-transplant. The hypothesis testing was conducted at the one-sided significant level of 0.05.

The secondary endpoints included the following:

- Utilization rate of DCD donor hearts, defined as the proportion of eligible DCD donor hearts that met the warm ischemic time limit of ≤ 30 minutes and were instrumented on the OCS Heart System that met the acceptance criteria for transplantation after OCS Heart System preservation.
- Incidence of HGRSAEs in the first 30 days post-transplant, defined as the following adverse events (at most one per type):
  - Moderate or severe PGD (left or right ventricle [LV or RV]; not including rejection or cardiac tamponade) according to the International Society for Heart and Lung Transplantation (ISHLT) consensus document (Kobashigawa, et al. 2014).
  - Primary graft failure requiring re-transplantation.
- Patient and graft survival at 30 days post-transplant.
- Patient and graft survival at 30 days or initial hospital discharge, if later than 30 days.
- Severe PGD (LV or RV; not including rejection or cardiac tamponade) according to the ISHLT consensus document.
- Use of MCS for > 72 hours immediately post-transplant in the DCD heart transplant patients.
- Patient survival at 1 year post-transplant in the DCD and SOC (SOC1 + SOC2) heart transplant patients, respectively. Data for the SOC heart transplant patients were obtained through the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplantation Network (OPTN) database.

B. Accountability of PMA Cohort

Randomized patients were enrolled between December 1, 2019, and November 11, 2020, at 13 investigational sites in the U.S. The database for this application reflected data collected through December 13, 2021.

At the time of database lock, a total of 101 DCD donor hearts were preserved using the OCS Heart System and 303 patients enrolled in the study. The disposition of the donor hearts is summarized in Figure 4. Out of the 303 patients, 297 were randomized, including 226 to the DCD Heart Possible group and 71 to the SOC Only group. Within the DCD Heart Possible group, 90 patients received a DCD heart preserved using the OCS Heart System and 62 received an SOC heart. Of the 71 patients randomized to SOC Only group, 28 were transplanted. In all, 90 patients each received a DCD heart and an SOC heart. The recipient enrollment consort diagram is shown in Figure 5.

Figure 4: Disposition of DCD Donor Hearts

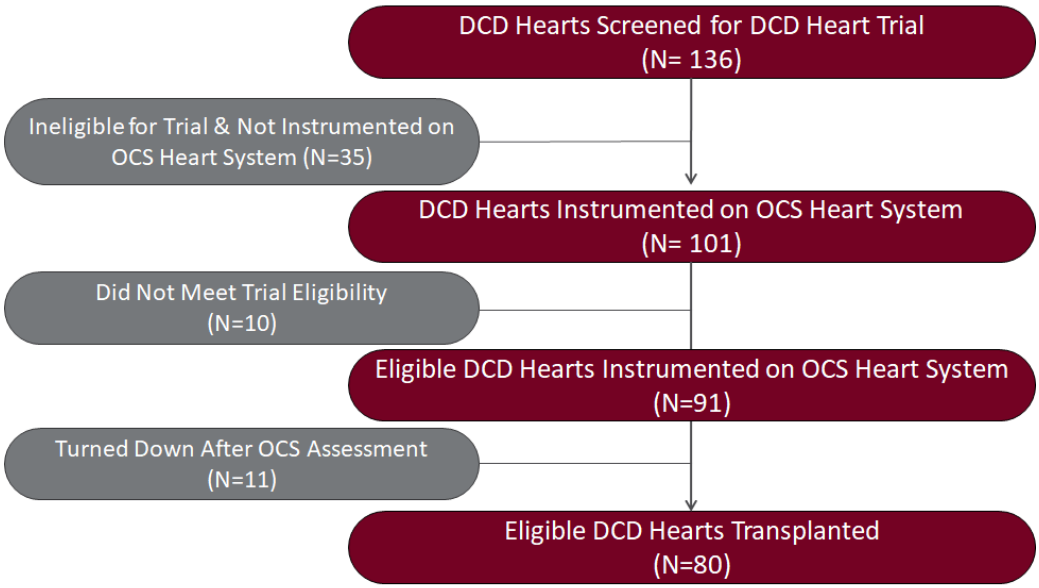
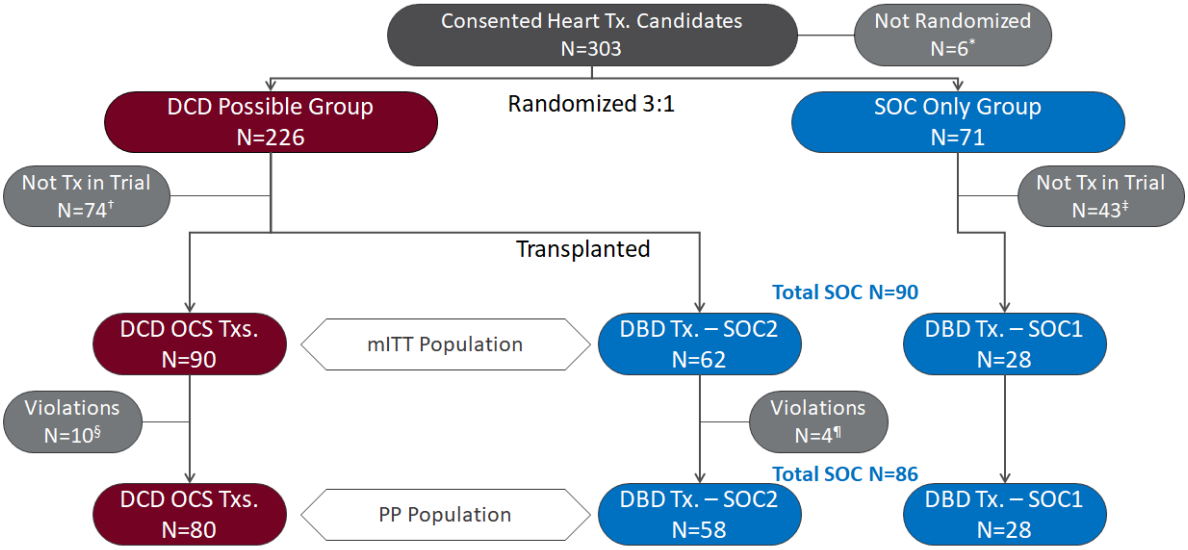


Figure 5: Recipient Enrollment Consort Diagram



*Enrolled after the randomization was stopped.
†Including 59 patients still on waitlist at the end of the trial, 6 patients withdrawn and transplanted in another trial, 3 patients who became ineligible prior to transplant, 3 patients who died on the waitlist, and 3 patients who withdrew consent.
‡Including 32 patients still on waitlist at the end of the trial, 7 patients withdrawn and transplanted in another clinical trial, 1 patient who became ineligible prior to transplant, 1 patient died on the wait list, and 2 patients delisted for transplant.
§Including 3 with donor age <18 years, 6 with warm ischemic time >30 mins, and 1 with continuously increasing lactate.
¶Including 4 donor age < 18 years.

The main analysis populations included the Per Protocol (PP) Population and the Modified Intent-to-Treat (mITT) Population, as defined in Table 1. The PP Population was the prespecified primary analysis population.

Table 1: Analysis Populations

Population	Definition	DCD Group	SOC Group (SOC1+SOC2)
Modified Intent-to-Treat (mITT) population	All randomized patients who were transplanted	90	90
Per Protocol (PP) population	All randomized patients who were transplanted and had no major protocol violations	80	86

C. Study Population Demographics and Baseline Parameters

Donor Demographics and Baseline Characteristics

The donor demographics and baseline characteristics are summarized in Table 2 for the donor hearts transplanted in the mITT population. The DCD heart donors were slightly younger than the SOC (DBD) heart donors, and there were more males and more that died from "anoxia-other" in the DCD heart donors than those in the SOC heart donors.

Table 2: Donor Demographics and Baseline Characteristics – Transplanted in the mITT Population

Parameter	Summary Statistics*		p-value†
	DCD Group (N=90)	SOC Group (N=90)	
Age (years)‡			0.0076
Mean ± SD	29.30 ± 7.50	33.18 ± 11.37	
Median	28.95	31.20	
Minimum - maximum	15.7 - 47.0	12.3 - 65.3	
Age ≥ 55 Years			0.2458
n (%)	0 (0.0)	3 (3.3)	
Gender			0.0029
Female - n (%)	6 (6.7)	21 (23.3)	
Male - n (%)	84 (93.3)	69 (76.7)	
Body mass index (kg/m^2)			0.1824
Mean ± SD	27.27 ± 6.15	28.54 ± 6.53	
Median	26.20	26.95	
Minimum - maximum	17.9 - 49.7	16.9 - 47.6	
Cause of death			0.0094
Cerebrovascular hemorrhage - n (%)	4 (4.4)	12 (13.3)	
Head trauma - n (%)	38 (42.2)	40 (44.4)	
Anoxia-drug overdose - n (%)	17 (18.9)	21 (23.3)	
Anoxia-other§ - n (%)	30 (33.3)	13 (14.4)	
Other¶ - n (%)	1 (1.1)	4 (4.4)	
Did the donor experience cardiac arrest?			0.8805
Yes - n (%)	51 (57.3)	50 (55.6)	
No - n (%)	38 (42.7)	40 (44.4)	
Estimated duration of cardiac arrest (mins)			0.2040
n	29	22	
Mean ± SD	21.4 ± 14.55	27.5 ± 19.43	
Median	18.0	26.0	
Minimum - maximum	0 - 60	1 - 61	

Parameter	Summary Statistics*		p-value†
	DCD Group (N=90)	SOC Group (N=90)	

*Percentages are calculated based on the number of donors with non-missing data in the given population.
†p-value from a two-sided, two-sample t-test for continuous variables or from a two-sided Fisher's Exact test for categorical variables, testing for a difference between the DCD and SOC groups.
‡Age = (Date of donor acceptance - date of birth)/365.25.
§"Anoxia-other" includes suicide by hanging, drowning, seizure, etc.
¶Other cause of death: cardiac arrest for the DCD group; traumatic cardiac arrest, cerebrovascular accident (stroke), trauma, trauma-electrical for the SOC group.

Recipient Demographics and Baseline Characteristics

The recipient demographics and baseline characteristics are summarized in Table 3 for the mITT population, which are typical for a heart transplant study performed in the U.S. The DCD and the SOC groups were similar in all parameters except for age, UNOS allocation status at time of transplant, the presence of MCS pre-transplant. Patients in the DCD group were slightly younger than those in the SOC group. The DCD group had more Status 4 patients, while the SOC group had more Status 2 patients at the time of transplant. In addition, more patients in the DCD group had a left ventricular assist device (LVAD) pre-transplant, while more patients in the SOC group had an intra-aortic balloon pump (IABP) placed pre-transplant.

Table 3: Recipient Demographics and Baseline Characteristics - mITT Population

Parameter	Summary Statistics		p-value*
	DCD Group (N=90)	SOC Group (N=90)	
Age (years)†			0.0409
Mean ± SD	51.31 ± 12.58	54.99 ± 11.39	
Median	53.95	57.60	
Minimum - maximum	20.0 - 73.1	22.3 - 73.9	
Age ≥ 65 years			0.5491
n (%)	13 (14.4)	17 (18.9)	
Gender			1.0000
Female - n (%)	24 (26.7)	24 (26.7)	
Male - n (%)	66 (73.3)	66 (73.3)	
Female donor to male recipient			0.1177
n (%)	1 (1.1)	6 (6.7)	
Body mass index (kg/m^2)			0.9402
Mean ± SD	29.63 ± 5.08	29.57 ± 5.25	
Median	29.30	29.20	
Minimum - maximum	19.2 - 40.6	15.9 - 43.5	
Baseline panel reactive antibody (%)			0.7467
Mean ± SD	8.3 ± 20.16	9.3 ± 22.19	

Parameter	Summary Statistics		p-value*
	DCD Group (N=90)	SOC Group (N=90)	
Median	0.0	0.0	
Minimum - maximum	0 - 87	0 - 91	
Primary etiology of heart failure diagnosis, n (%)			0.9694
Ischemic cardiomyopathy	21 (23.3)	22 (24.4)	
Congenital heart disease	8 (8.9)	5 (5.6)	
Restrictive cardiomyopathy	2 (2.2)	3 (3.3)	
Dilated cardiomyopathy	17 (18.9)	16 (17.8)	
Non-ischemic Cardiomyopathy	40 (44.4)	42 (46.7)	
Other‡	2 (2.2)	2 (2.2)	
Presence of mechanical circulatory support pre-transplant, n (%)	58 (64.4)	64 (71.1)	0.4253
Left ventricular assist device (LVAD)	44 (48.9)	27 (30.0)	0.0144
Right ventricular assist device (RVAD)	0 (0.0)	2 (2.2)	
Bi-ventricular assist device (BiVAD)	0 (0.0)	2 (2.2)	
Extracorporeal membrane oxygenation (ECMO)	0 (0.0)	4 (4.4)	
Intra-aortic balloon pump (IABP)	14 (15.6)	38 (42.2)	0.0001
Artificial Heart	0 (0.0)	0 (0.0)	
UNOS heart allocation status on day of transplant, n (%)			<0.0001
Status 1	1 (1.1)	5 (5.6)	
Status 2	18 (20.0)	47 (52.2)	
Status 3	16 (17.8)	15 (16.7)	
Status 4	43 (47.8)	14 (15.6)	
Status 5	0 (0.0)	0 (0.0)	
Status 6	12 (13.3)	9 (10.0)	
Presence of mechanical ventilation on the day of transplant, n (%)	0 (0.0)	0 (0.0)	-
History of diabetes	31 (34.4)	28 (31.1)	
History of renal dysfunction	3 (3.3)	2 (2.2)	

*p-value from a two-sided, two-sample t-test for continuous variables or from a two-sided Fisher's Exact test for categorical variables, testing for a difference between the DCD and SOC.

†Age = (Date of transplant - date of birth)/365.25.

‡Other included: muscular dystrophy and post-partum cardiomyopathy for the DCD group; cardiogenic shock and arrhythmogenic right ventricular cardiomyopathy for the SOC group.

D. Safety and Effectiveness Results

1. Primary Endpoint

The analysis of the primary endpoint is summarized in Table 4 for the PP population and mITT population. The adjusted patient survival rate at 6 months post-transplant in the PP Population (the prespecified primary analysis population) was 93.7% in the DCD group and 90.4% in the SOC group, with a difference of -3.2% (95% CI: -9.8%, 3.4%). Since the upper bound of the 90% confidence interval of the difference was less than the non-inferiority margin of 20%, the primary endpoint was met, which was further corroborated by the mITT analysis. The results of the primary endpoint are shown in Figure 6.

Table 4: Analyses of the Primary Endpoint

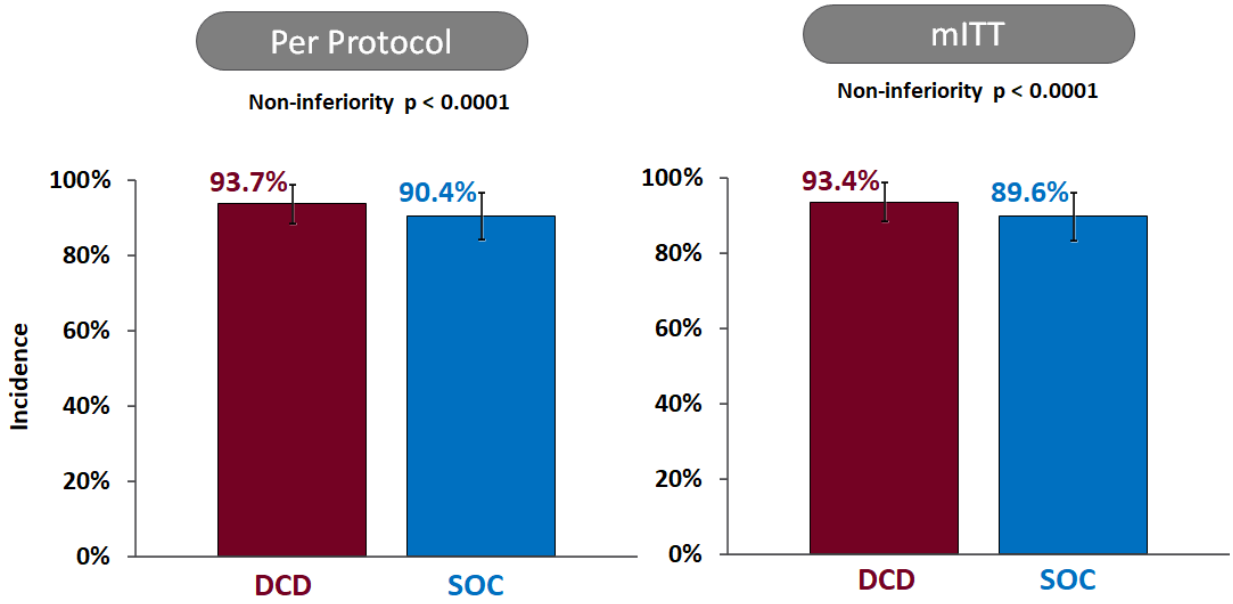
Variable	PP Analysis		mITT Analysis	
	DCD	SOC	DCD	SOC
Total # of patients	80	86	90	90
Total # of patients included in the analysis*	80	84	90	88
Patient survival at 6 months post-transplant	76	75	85	78
Success rate at 6 months (unadjusted)	95.0%	89.3%	94.4%	88.6%
Success rate at 6 months (adjusted†)	93.7%	90.4%	93.4%	89.6%
Difference (SOC-DCD): adjusted	-3.2%		-3.9%	
90% confidence interval	[-9.8%, 3.4%]		[-10.9%, 3.2%]	
Non-inferiority limit	20%		20%	
p-value‡	<0.0001		<0.0001	
Non-inferiority test	Passed		Passed	

*Two patients in the SOC group were retransplanted on day 5 and day 7, respectively, after the first transplant and were excluded from the analysis.

†Adjusted percentages are based on a linear probability model, with the following terms in the model: treatment, ischemic time ≥ 4 hours (Y/N) and mechanical circulatory support pre-transplant (Y/N).

‡The one-sided p-value for the test of the null hypothesis was obtained based on a statistic for the difference (SOC-DCD) in least squares means for each treatment minus the non-inferiority margin of 0.20, divided by the standard error of the difference in the least squares means, assuming an approximate normal distribution.

Figure 6: Primary Endpoint Results Adjusted for Risk Factors

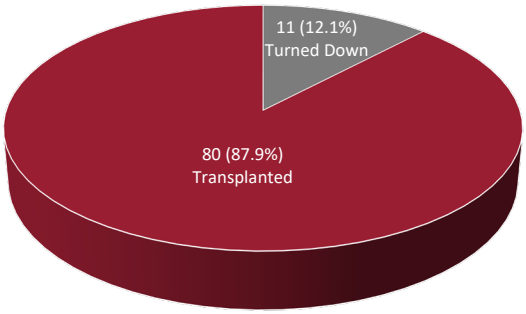


2. Secondary Endpoints

Utilization Rate of DCD Donor Hearts

Of the DCD donor hearts instrumented and preserved on the OCS Heart System, 91 met the trial eligibility, 80 of which were transplanted. Thus, the DCD heart utilization rate was 87.9% (80/91), as illustrated in Figure 7.

Figure 7: Utilization Rate of Eligible DCD Donor Hearts



HGRSAEs

The HGRSAEs within 30 days post-transplant in the mITT population are summarized in Table 5. The average number of HGRSAEs per patient within the first 30 days was 0.2 for the DCD group compared to 0.1 for the SOC group. More patients in the DCD group experienced moderate or severe PGD (20.0%) compared to the SOC group (9.1%). However, more patients in the SOC group had primary graft failure (2.2%) than those in the DCD patients (0.0%).

Table 5: HGRSAEs Within 30 Days Post-transplant - mITT Population

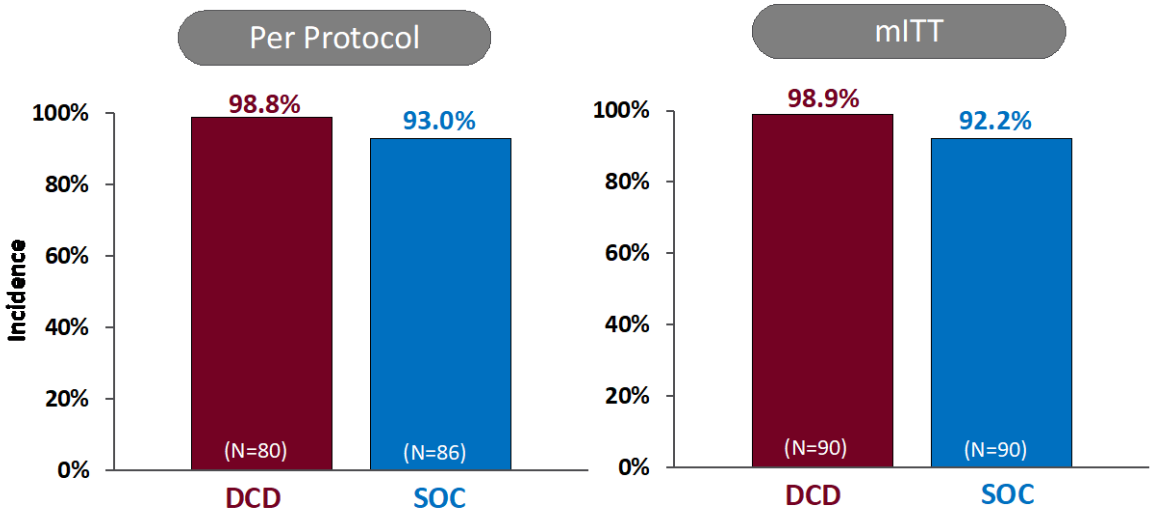
Parameter	DCD Group (N=90)	SOC Group (N=88*)
Number of HGRSAEs in the first 30 days post-transplantation per patient†		
• Mean	0.2	0.1
• Median	0.0	0.0
• SD	0.40	0.38
• Minimum - maximum	0 - 1	0 - 2
HGRSAEs by type, n/N (%)		
• Moderate or severe PGD (LV or RV)	18/90 (20.0)	8/88 (9.1)
○ LV moderate PGD	5/90 (5.6)	4/88 (4.5)
○ LV severe PGD	12/90 (13.3)	4/88 (4.5)
○ RV PGD	1/90 (1.1)	0/88 (0.0)
• Primary graft failure requiring re-transplantation	0/90 (0.0)	2/90 (2.2)

*One study site did not provide the data on 2 patients in the SOC group.
†Patients with both LV moderate or severe PGD and RV PGD were counted as having one event.

Patient and Graft Survival at 30 Days Post-transplant

Patient and graft survivals at 30 days post-transplant in the DCD group are shown in Figure 8 for the PP and mITT populations. In the PP population, the patient and graft survival rate at 30 days was 98.8% in the DCD group compared to 93.0% in the SOC group. The result for the mITT population was similar (98.9% vs. 92.2%).

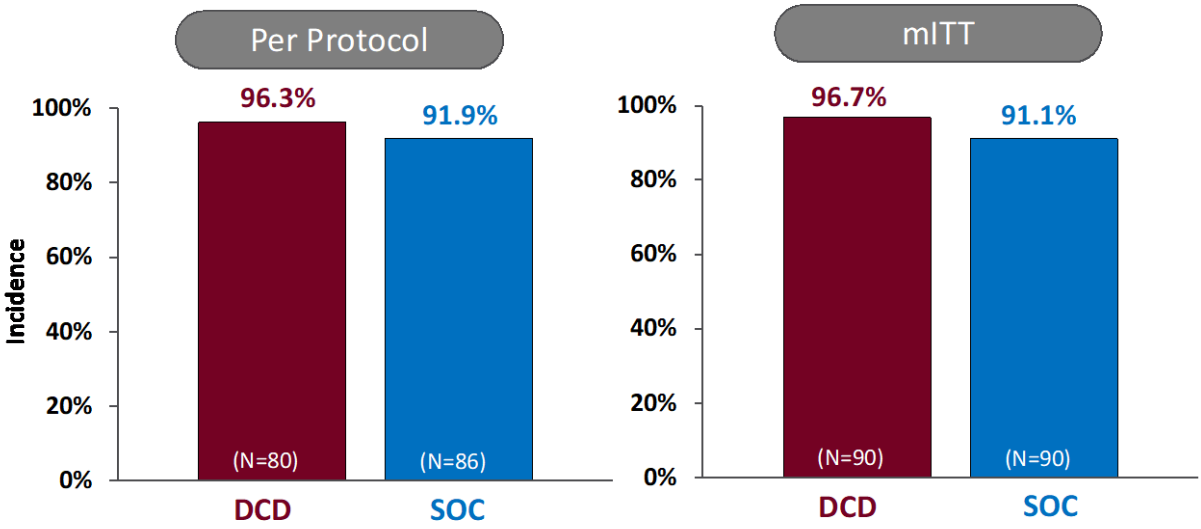
Figure 8: Patient and Graft Survival at 30 Days Post-transplant



Patient and Graft Survival at 30 Days Post-transplant or Initial Hospital Discharge, if Later Than 30 Days

Patient and graft survivals at day 30 or initial hospital discharge (if later than 30 days) were 96.3% in the DCD group and 91.9% in the SOC group in the PP population, as summarized in Figure 9. The results were similar in the mITT population (96.7% vs. 91.1%).

Figure 9: Patient and Graft Survival at 30 Days or Initial Hospital Discharge, if Later Than 30 Days



Severe PGD

In the PP population, the incidences of severe PGD as defined by the ISHLT consensus criteria were 16.3% and 4.8% in the DCD group and SOC group, respectively; in the mITT population, the incidences were 14.4% and 4.5%, respectively, as summarized in Table 6.

Table 6: Severe PGD Within 24 Hours

Severe PGD	Summary Statistics*	
	DCD Group	SOC Group
PP population	13/80 (16.3)	4/84 (4.8)
mITT population	13/90 (14.4)	4/88† (4.5)

*n/N (%)
†One study site did not provide the data on 2 patients in the SOC group.

Use of MCS for > 72 Hours Immediately Post-transplant (DCD Group Only)

In the PP population, 13.8% of patients in the DCD group had MCS for greater than 72 hours immediately post-transplant, while in the mITT population, the proportion was 13.3%, as summarized in Table 7.

Table 7: Use of MCS for > 72 Hours Immediately Post-transplant - DCD Group Only

Use of MCS for > 72 hours immediately post-transplant	Summary Statistics*
PP population	11/80 (13.8)
mITT population	12/90† (13.3)

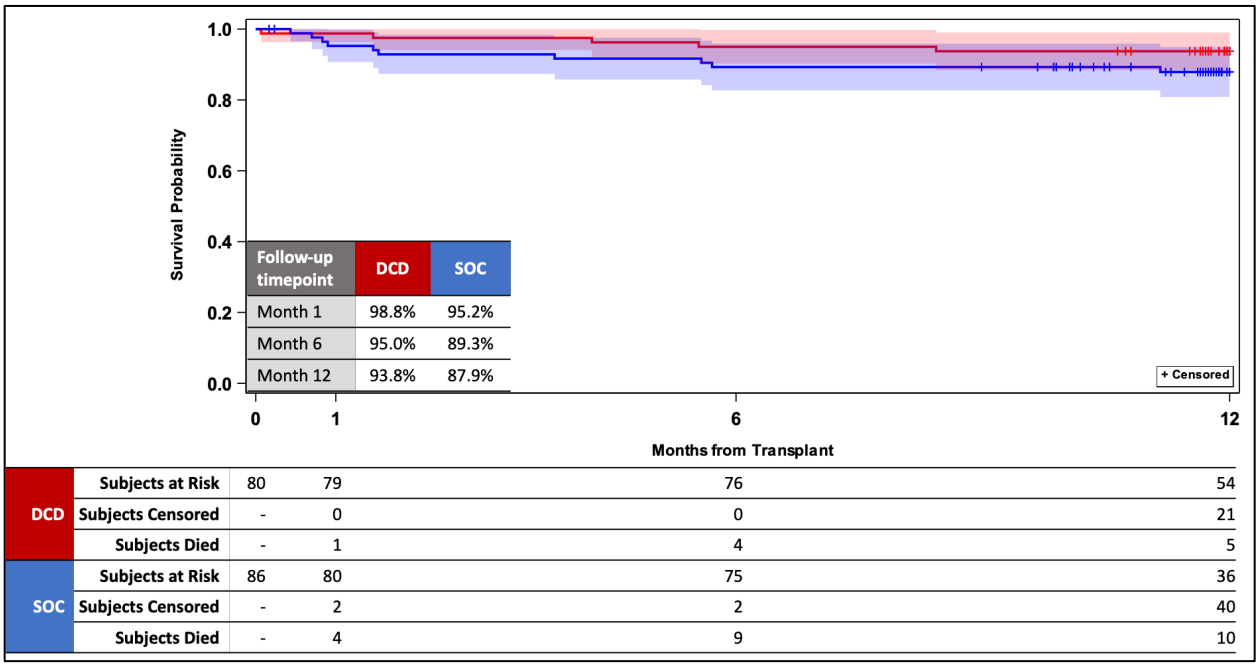
*n/N (%)

†Of the 12 patients, 7 had severe PGD adjudicated by the CEC and 5 did not have severe PGD but had IABPs placed: 3 for center specific protocol (prophylactic) and 2 for cardiac support (graft dysfunctions not meeting the PGD criteria).

Patient Survival at 1 Year Post-transplant

The Kaplan-Meier (KM) analysis of patient survival through 1 year post-transplant are shown in Figure 10. The patient survival rate was 93.8% in the DCD group and 87.9% in the SOC group.

Figure 10: Patient Survival Through 1 Year Post-transplant - PP Population



3. Other Study Observations

Adverse Events

The comprehensive list of all CEC-adjudicated serious adverse events (SAEs) observed through 30 days post-transplant in the DCD group is shown in Table 8.

Table 8: CEC-adjudicated SAEs Observed Through 30 Days in the DCD Group - mITT Population

SAEs by System Organ Class/Preferred Term	Summary Statistics*	
	Patients	Events
Any SAEs	67 (74.4)	133 (100.0)
Blood and lymphatic system disorders	3 (3.3)	3 (2.3)
Anemia	1 (1.1)	1 (0.8)
Coagulopathy	2 (2.2)	2 (1.5)
Cardiac disorders	34 (37.8)	38 (28.6)
Arrhythmia supraventricular	1 (1.1)	1 (0.8)
Atrial fibrillation	1 (1.1)	1 (0.8)
Atrial flutter	2 (2.2)	2 (1.5)
Cardiac arrest	1 (1.1)	1 (0.8)
Cardiac tamponade	2 (2.2)	2 (1.5)
Cardiogenic shock	2 (2.2)	2 (1.5)
Left ventricular dysfunction	16 (17.8)	16 (12.0)
Pericardial effusion	4 (4.4)	4 (3.0)
Pericardial hemorrhage	1 (1.1)	1 (0.8)
Right ventricular dysfunction	6 (6.7)	6 (4.5)
Supraventricular tachycardia	1 (1.1)	1 (0.8)
Tricuspid valve incompetence	1 (1.1)	1 (0.8)
Gastrointestinal disorders	4 (4.4)	5 (3.8)
Diarrhea	1 (1.1)	1 (0.8)
Gastrointestinal necrosis	2 (2.2)	2 (1.5)
Intestinal ischemia	1 (1.1)	1 (0.8)
Volvulus	1 (1.1)	1 (0.8)
Immune system disorders	18 (20.0)	19 (14.3)
Transplant rejection	18 (20.0)	19 (14.3)
Infections and infestations	12 (13.3)	12 (9.0)
Bacteremia	2 (2.2)	2 (1.5)
Endocarditis	1 (1.1)	1 (0.8)
Fungal infection	1 (1.1)	1 (0.8)
Nasopharyngitis	1 (1.1)	1 (0.8)
Pneumonia	5 (5.6)	5 (3.8)
Sepsis	2 (2.2)	2 (1.5)
Injury, poisoning and procedural complications	3 (3.3)	3 (2.3)
Iatrogenic injury	1 (1.1)	1 (0.8)
Traumatic hemothorax	2 (2.2)	2 (1.5)
Metabolism and nutrition disorders	1 (1.1)	1 (0.8)
Hyperkalemia	1 (1.1)	1 (0.8)
Musculoskeletal and connective tissue disorders	1 (1.1)	1 (0.8)
Flank pain	1 (1.1)	1 (0.8)
Nervous system disorders	6 (6.7)	6 (4.5)
Brain hypoxia	1 (1.1)	1 (0.8)

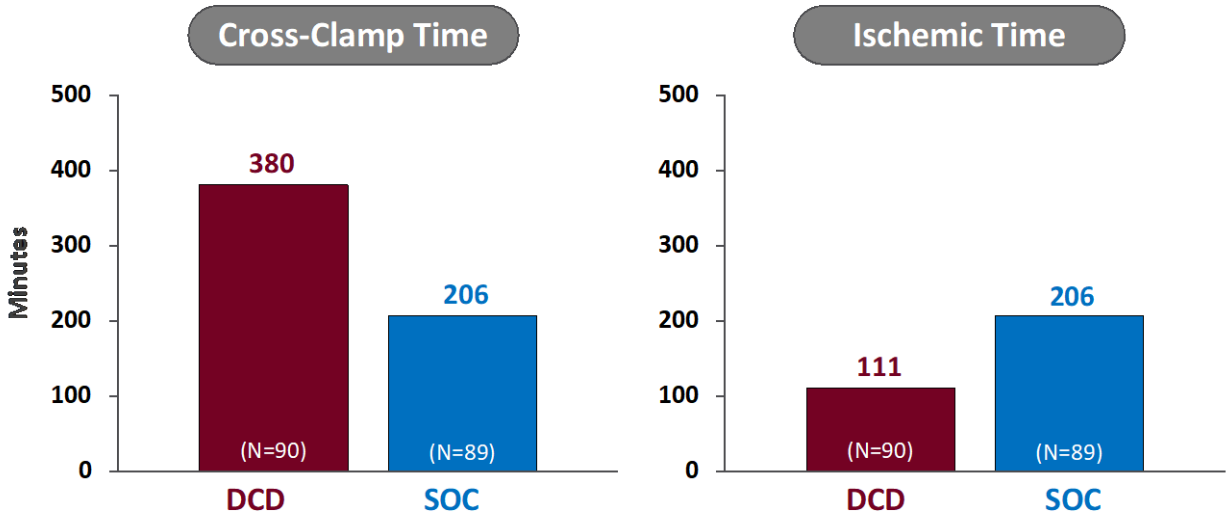
SAEs by System Organ Class/Preferred Term	Summary Statistics*	
	Patients	Events
Ischemic stroke	1 (1.1)	1 (0.8)
Migraine	1 (1.1)	1 (0.8)
Seizure	2 (2.2)	2 (1.5)
Spinal stroke	1 (1.1)	1 (0.8)
Psychiatric disorders	2 (2.2)	2 (1.5)
Delirium	2 (2.2)	2 (1.5)
Renal and urinary disorders	19 (21.1)	19 (14.3)
Acute kidney injury	15 (16.7)	15 (11.3)
Renal failure	4 (4.4)	4 (3.0)
Respiratory, thoracic and mediastinal disorders	11 (12.2)	11 (8.3)
Bronchial secretion retention	1 (1.1)	1 (0.8)
Hypoxia	1 (1.1)	1 (0.8)
Pleural effusion	3 (3.3)	3 (2.3)
Respiratory failure	6 (6.7)	6 (4.5)
Vascular disorders	13 (14.4)	13 (9.8)
Deep vein thrombosis	2 (2.2)	2 (1.5)
Hemodynamic instability	1 (1.1)	1 (0.8)
Hemorrhage	10 (11.1)	10 (7.5)

*n (%). Number of patients refers to the number of patients with at least one SAE of the indicated type. Number of events refers to all events of the indicated type. Patients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term. Percentages are calculated based on the total number of patients in the given population or the total number of events, as appropriate.

Total Cross-clamp Time and Ischemic Time

The mean cross-clamp time (time from cross-clamp application in the donor to the cross-clamp removal in the recipient) and ischemic time (time that a donor heart is ischemic without any oxygenated perfusion) for the donor hearts are shown in Figure 11. The mean cross-clamp time was longer in the DCD group than in the SOC group (380 vs. 206 minutes), while the mean ischemic time was shorter in the DCD group than in the SOC group (111 vs. 206 minutes).

Figure 11: Mean Cross-Clamp and Ischemic Times for Donor Hearts



OCS Heart System Perfusion Parameters for Transplanted DCD Hearts

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

Table 9: OCS Heart System Perfusion Parameters - mITT Population

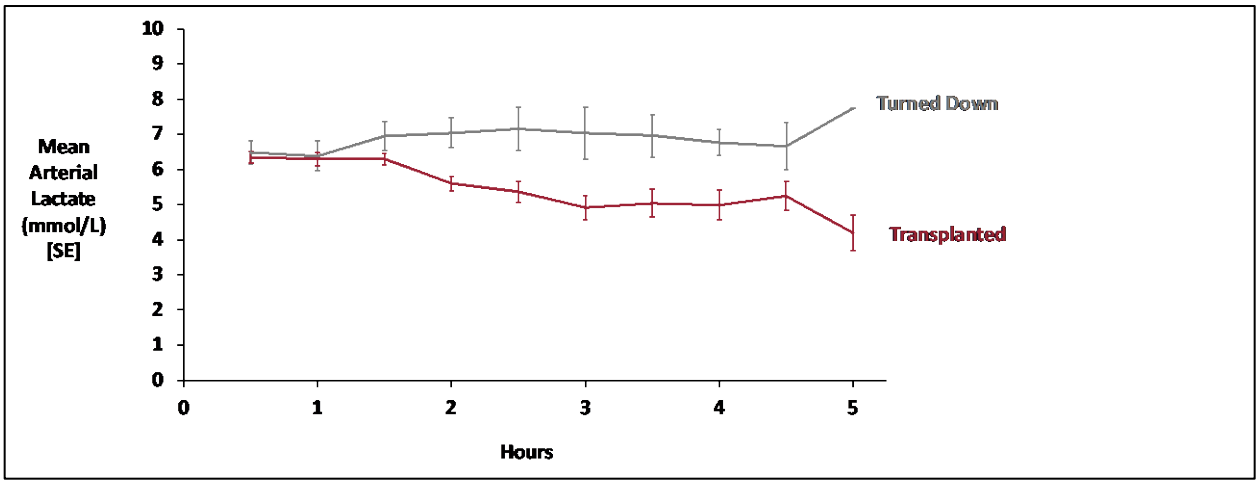
Parameter	Summary Statistics (N=90)
Perfusion time (mins)	
Mean ± SD	270.0 ± 65.01
Median	263.0
Minimum - maximum	104 - 472
Pump flow (L/min)	
Mean ± SD	1.086 ± 0.108
Median	1.065
Minimum - maximum	0.90 - 1.47
Coronary flow (L/min)	
Mean ± SD	0.714 ± 0.117
Median	0.720
Minimum - maximum	0.15 - 0.98
Aortic flow (L/min)	
Mean ± SD	1.105 ± 0.094
Median	1.095
Minimum - maximum	0.91 - 1.47
Aortic pressure (mmHg)	
Mean ± SD	72.0 ± 8.79

Parameter	Summary Statistics (N=90)
Median	74.0
Minimum - maximum	46 - 88

Donor Heart Turndowns Following OCS Heart System Preservation

Eleven (11) DCD donor hearts were turned down for transplantation following preservation on the OCS Heart System. The reasons for the turndowns were primarily rising lactate and/or other clinical factors related to the organ performance or condition as determined by the surgeons. The mean arterial lactate levels in the turned-down hearts were generally higher than those that were transplanted, as shown in Figure 12. Additionally, a decreasing arterial lactate trend was not achieved in the turned-down hearts as was the general case for the transplanted hearts.

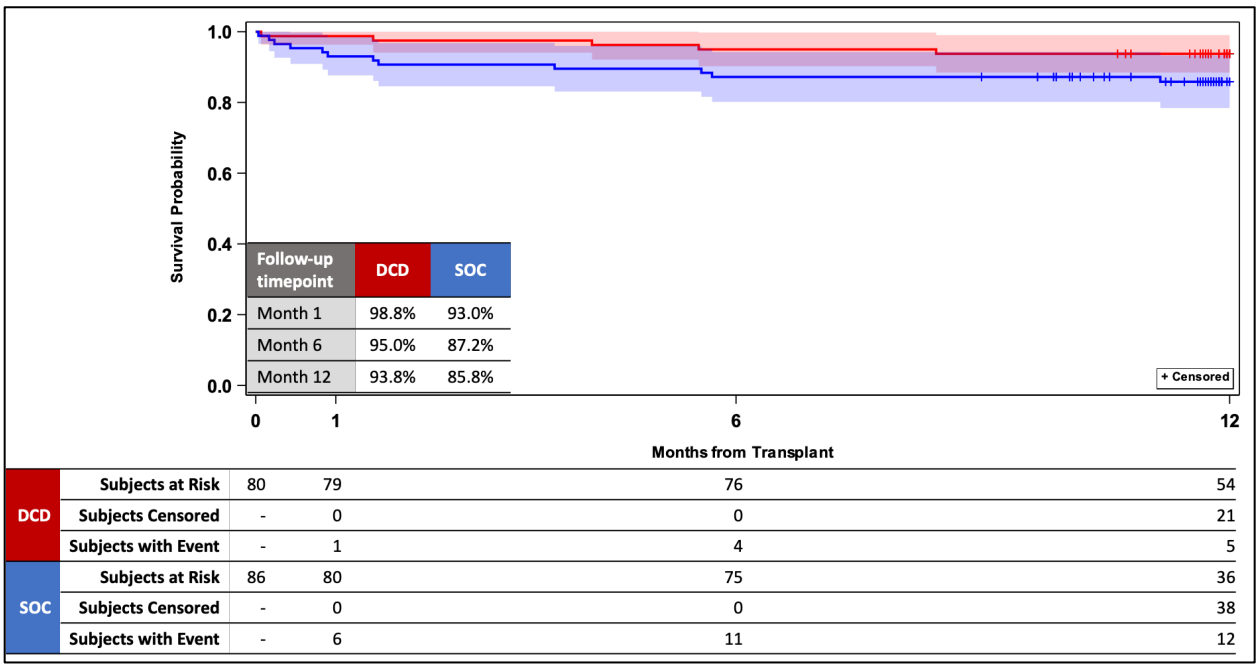
Figure 12: Mean Arterial Lactate Trend in DCD Donor Hearts on OCS Heart System



Patient and Graft Survival at 1 Year Post-transplant

The KM analysis of patient and graft survival through 1 year post-transplant is shown in Figure 13. The patient and graft survival rate was 93.8% in the DCD group compared to 85.8% in the SOC group.

Figure 13: Patient and Graft Survival Through 1 Year Post-transplant - PP Population



DCD	Subjects at Risk	80	79	76	54
	Subjects Censored	-	0	0	21
	Subjects with Event	-	1	4	5
SOC	Subjects at Risk	86	80	75	36
	Subjects Censored	-	0	0	38
	Subjects with Event	-	6	11	12

4. Pediatric Extrapolation

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

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 21 investigators and 102 sub-investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Device panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM CLINICAL STUDIES

A. Effectiveness Conclusions

In the DCD Heart Trial, the 6-month survival rate in recipients of a DCD donor heart preserved on the OCS Heart System was 93.7% (PP population), which was statistically non-inferior to that (90.4%, $p<0.0001$) of recipients of a DBD donor heart preserved using SOC cold storage, after adjustment for risk factors. Patient survival at 12 months was 93.8% in the DCD group compared to 87.9% in the SOC group (PP population).

The 30-day patient and graft survival rate was 98.8% in the DCD donor heart recipients and 93.0% in the DBD donor heart recipients (PP population). At 1 year post-transplant, the KM rates of patient and graft survival were 93.8% and 85.8% in the DCD and DBD donor heart recipients, respectively (PP population).

The utilization rate of the DCD donor hearts preserved on the OCS Heart System was 87.9%, which demonstrated the potential of the OCS Heart System to make more DCD donor hearts available for transplantation.

B. Safety Conclusions

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

In the DCD Heart Trial, the safety of the device was primarily assessed through the endpoint of HGRSAEs. In all the transplant recipients, the average number of HGRSAEs per patient was 0.2 in the first 30 days in the DCD group compared to 0.1 in the SOC group. Although more patients in the DCD group experienced moderate or severe PGD (20.0%) than in the SOC group (9.1%), more patients in the SOC group had primary graft failure requiring re-transplantation (2.2%) than in the DCD group (0.0%).

C. Benefit-Risk Determination

The probable benefits of preservation of DCD donor hearts using the OCS Heart System include utilization of donor hearts that otherwise would mostly not have been utilized due to the limitations of the cold storage method, thereby increasing the donor pool and allowing more heart transplants to be performed for patients on the waitlist.

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

1. Patient Perspectives

   This submission did not include specific information on patient perspectives.

In conclusion, given the available information above, the data support that the probable benefits of preservation of the DCD donor hearts using the OCS Heart System outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device for the *ex vivo* reanimation, functional monitoring, and beating-heart preservation of DCD hearts.

XIII. CDRH DECISION

CDRH issued an approval order on April 27, 2022. The final clinical conditions of approval cited in the approval order are described below.

The applicant must conduct two post-approval studies:

1. **Continued Follow-up of the DCD Heart Premarket Cohort**: This study should be conducted per the protocol, entitled "OCS DCD Heart + CAP Continued Follow-Up Post-Approval Study" (protocol number: OCS-HEART-03-PAS), dated March 31, 2022. The study will consist of all living patients who were enrolled under the IDE, including those enrolled under the Continued Access Protocol (CAP) investigation. The objective of the study is to characterize the clinical outcomes annually through 5 years post-transplant. The safety and effectiveness endpoints include patient survival, cardiac-related patient survival, graft survival, and patient and graft survival through 5 years post-transplant.

2. **Post-commercialization DCD Heart New Enrollment Study**: This study should be conducted per the protocol, entitled "OCS Heart Perfusion Post-Approval Registry Protocol" (protocol number: OCSHEART-01-ClinPAS), dated April 20, 2022. The study will enroll a total of 150 patients that constitute the Primary Analysis Population, at up to 40 U.S. heart transplant centers. The objective of the study is to characterize the performance of the OCS Heart System in the real-world setting, as compared to concurrent control data obtained from the United Network for Organ Sharing (UNOS) database for recipients of standard criteria donor hearts preserved using cold static cardioplegic storage. The primary endpoint of the study is patient survival at 1 year post-transplant. Other endpoints include patient/graft survival through 5 years post-transplant, incidence of moderate or severe primary graft dysfunction (PGD; left or right ventricle), and incidence of donor heart turndowns following OCS Heart System perfusion.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

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