STATISTICAL ANALYSIS PLAN

Protocol OCS-CAR-03202019

Clinical Trial to Evaluate the Safety and Effectiveness of the Portable Organ Care System (OCS™) Heart for Resuscitation, Preservation and Assessment of Hearts from Donors after Circulatory Death (DCD Heart Trial)

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Study Number: OCS-CAR-03202019

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List of Abbreviations

Term	Definition
BiVAD	Bilateral Ventricular Assist Device
BMI	Body Mass Index
BTT	Bridge to Transplant
CEC	Clinical Events Committee
CI	Confidence Interval
DBD	Donor after Brain Death
DCD	Donor after Circulatory Death
ECMO	Extracorporeal Membrane Oxygenation
EVHP	Ex-Vivo Heart Perfusion
HGRSAE	Heart Graft-Related Serious Adverse Event
IABP	Intra-aortic Balloon Pump
ICU	Intensive Care Unit
ISHLT	International Society for Heart and Lung Transplantation
LVAD	Left Ventricular Assist Device
MCS	Mechanical Circulatory Support
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-treat
OCS	Organ Care System
OPTN	Organ Procurement and Transplantation Network
PGD	Primary Graft Dysfunction
PMA	Premarket Approval
RVAD	Right Ventricular Assist Device
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	Standard of Care
T0, T24, T72	Time after transplant (0, 24, 72 hours)
UNOS	United Network for Organ Sharing
US	United States
WIT	Warm Ischemic Time

1.0 INTRODUCTION

This analysis plan provides a detailed description of the safety and effectiveness analyses (and associated summary tables) planned in the analysis of data in the OCS-CAR-03202019 study "Clinical Trial to Evaluate the Safety and Effectiveness of The Portable Organ Care System (OCS™) Heart for Resuscitation, Preservation and Assessment of Hearts from Donors after Circulatory Death (DCD Heart Trial)".

2.0 STUDY OBJECTIVE

The objective of the DCD Heart Trial is to evaluate the effectiveness of the OCS Heart System to resuscitate, preserve, and assess hearts donated after circulatory death for transplantation, and to ultimately increase the pool of donor hearts available for transplantation.

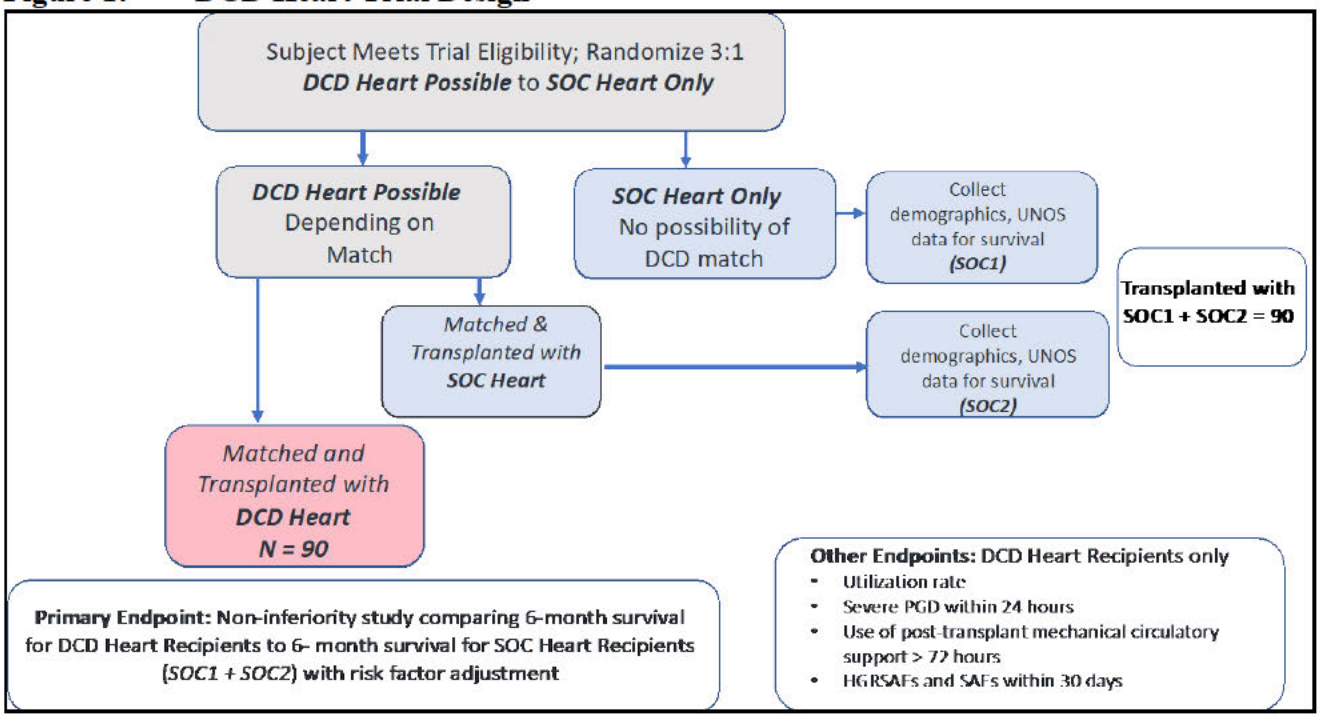
A secondary objective is to evaluate the safety and effectiveness of transplanting DCD hearts preserved on the OCS Heart System compared to transplantation with Donor after Brain Death (DBD) hearts preserved with SOC.

3.0 STUDY DESIGN

3.1 Overview

This is a prospective, randomized and concurrent controlled, non-inferiority pivotal trial in which subjects who receive a DCD donor heart transplant will be compared to subjects who receive a standard of care (SOC) donor heart transplant, regardless of whether those subjects were randomized to receive an SOC donor heart (SOC1) or to potentially receive a DCD donor heart (SOC2). The primary effectiveness comparison between these groups is analyzed by actual treatment and includes adjustment for differences in risk factors. The trial design is illustrated in Figure 1 below.

Figure 1: DCD Heart Trial Design



The trial will be conducted at a maximum of 25 participating sites with 90 transplanted DCD heart recipients and 90 SOC heart transplant recipients. Follow-up data for the SOC recipients will be obtained from the UNOS/OPTN standard database for U.S. transplant recipients through five years after transplantation.

Subjects who receive a DCD heart transplant will be followed for 12 months from the date of transplantation. Data from UNOS/OPTN transplantation database will be obtained through five years after transplant.

The Schedule of Clinical Assessments for the donor and recipient is provided in Table 1.

Table 1. Schedule of Clinical Assessments

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

Evaluations	DCD Transplanted Recipient Schedule of Assessments							
	Day of Tx	T0[a]	T24	T72	Initial Hospital Discharge	Day 30	Mo 6[c]	Mo 12[d]
Eligibility & Informed Consent	X							
Demographics/ Characteristics	X							
Medical & Cardiac History	X							
Transplant Details	X							
PGD Scores			X					
Inotropic Support		X	X					
Right Heart Catheter Results		X[b]	X[b]					
Mechanical Circulatory Support		X	X	X				
Patient & Graft Survival		X	X	X	X	X	X	X
Echocardiogram			X					
Initial ICU Stay					X			
Initial Hospital Stay					X			
HGRSAEs and SAEs	X	X	X	X		X		
Cardiac Allograft Vasculopathy								X[b]

a T0 is defined as the time of initial admission to ICU immediately post-heart transplant procedure.
b ONLY Tests regularly scheduled per center standard of care or performed due to a clinical cause at these timepoints will be collected.
c Six month follow-up window is ± 30 days.
d Twelve month follow-up window is ± 60 days.

3.2 Method of Assigning Subjects to Treatment

Primary heart transplant candidates will be screened for trial eligibility. Every eligible candidate will be asked to participate. Consented subjects will be randomized into two groups: ***DCD Heart Possible*** and ***SOC Heart Only*.**

Subjects who are randomized into the ***SOC Heart Only*** group will have no possibility for a DCD Heart transplant. Subjects randomized into the ***DCD Heart Possible*** group have the possibility of receiving either a DCD heart or an SOC donor heart, depending upon the donor match. In order to obtain enough subjects with DCD donor heart transplants, subjects will be randomized 3:1 to the ***DCD Heart Possible*** and ***SOC Heart Only*** arms, respectively. Eligible subjects in the ***SOC Heart Only*** group who are transplanted will form one ***SOC Heart Transplanted Recipient group (SOC1*)**. In the ***DCD Heart Possible*** arm, if a screened and eligible subject is matched with an SOC donor heart before an eligible DCD donor heart becomes available and is transplanted, these subjects will form a second ***SOC Heart Transplanted Recipient group (SOC2*)**.

Note: After completing enrollment there were 6 cases in which a SOC donor heart was transplanted without randomization. These subjects' data will be included in data listings and in ad-hoc analyses to support the final clinical study report.

3.3 Blinding

This is an open label study. However, the SOC 6-month primary endpoint survival data will be blinded to the statistical group until the database hard-lock.

3.4 Determination of Sample Size

We have assumed that transplantation of a DCD donor heart will be an infrequent event and that there will be at least a 1:1 ratio of SOC heart transplants to DCD heart transplants, despite the 3:1 randomization to the ***DCD Heart Possible*** and ***SOC Heart Only*** groups. The sample size calculations were based on the following specifications:

- Non-inferiority study with comparison of DCD heart transplanted recipients to SOC heart transplanted recipients
- Primary endpoint is patient survival at 6 months post-transplant
- One-sided normal approximation test
- Alpha = 0.05
- Power = 80%
- Assume 1:1 occurrence of SOC heart transplants (SOC1 and SOC2) and DCD heart transplants
- True SOC survival percentage = 93%
- True DCD survival percentage = 85%
- Non-inferiority margin = 20%.

Based on these assumptions, a sample size of 84 DCD heart transplanted recipients and at least 84 SOC heart transplanted recipients will provide at least 80% power. This sample size was increased to

90 per group to reflect potential enrollment of subjects who are lost to follow-up, withdraw or do not meet eligibility criteria.

3.5 Changes to the Protocol-Specified Analyses

The protocol proposed stopping enrollment once the DCD heart transplanted recipients enrollment target (N=90) was met. Further, if the enrollment target in the SOC heart transplanted recipient population had not been met, a propensity-score-matched subset of subjects from the UNOS database was proposed to supplement the set of subjects in the SOC Heart Transplanted Recipient Population at the time of the last DCD transplant. However, in communications with FDA it became clear that FDA strongly preferred prospective enrollment of 90 SOC subjects rather than the propensity matched approach outlined in the protocol. Therefore, the statistical analysis will be performed using the 90 DCD and 90 SOC subjects that were prospectively enrolled without propensity-matched subjects from UNOS.

The protocol stated that the analysis of the primary effectiveness endpoint would be adjusted for known donor and recipient risk factors (defined in section 12.1) for mortality, and any of the baseline and demographic characteristics identified as potential risk factors for which there is a statistically significant difference between the treatment groups. This SAP clarifies that the primary effectiveness analysis will be adjusted for known donor and recipient risk factors for mortality, but not for baseline and demographic characteristics identified as potential risk factors.

The protocol stated that statistical testing will be performed for the comparisons of recipient demographics and baseline characteristics and of patient survival at 6 months for the following groups: SOC1 vs SOC2, DCD Heart vs SOC1, DCD Heart vs SOC2. Only summary statistics will be provided for those comparisons.

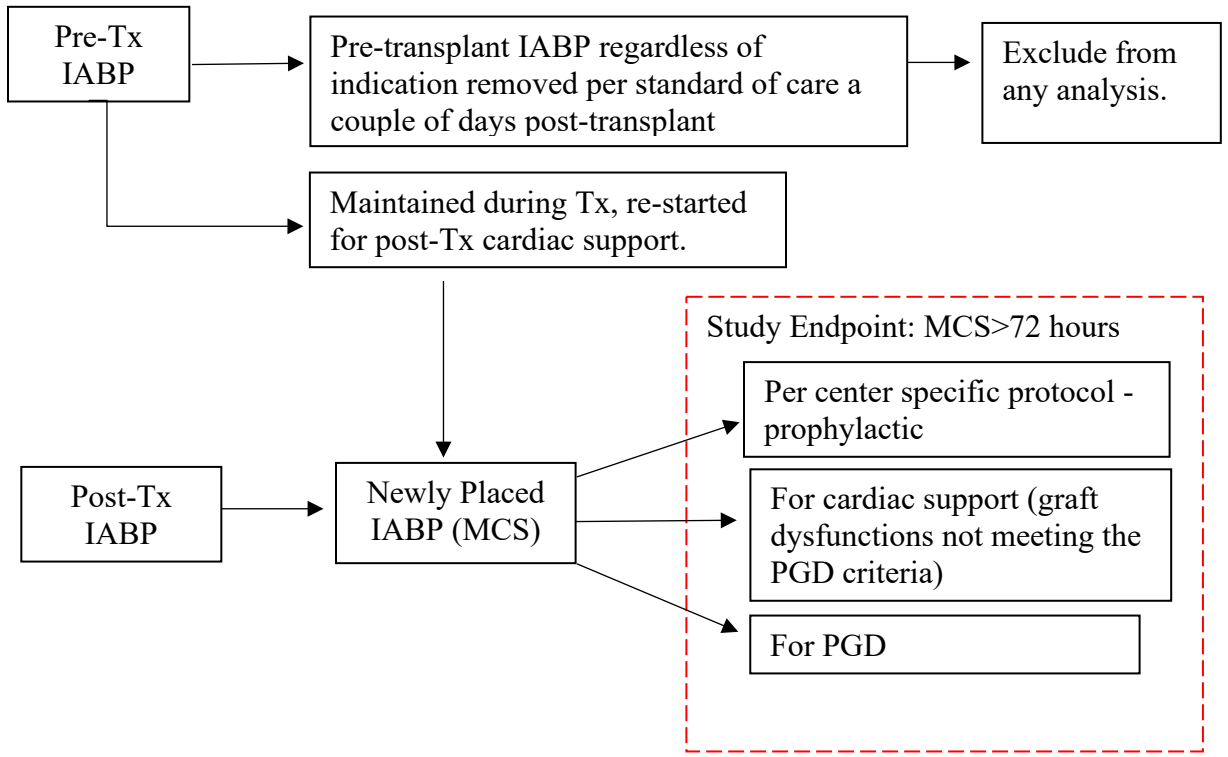
Sensitivity analyses of the primary effectiveness endpoint were not described in the protocol and have been added to the SAP. First, an unadjusted analysis will be performed with the same non-inferiority margin as recommended by the FDA. Additionally, a tipping point analysis will be performed without risk factor adjustment using the Wald method, in which subjects with unsuccessful or missing outcomes in the SOC Heart Transplanted Recipient Population will have successful outcomes imputed iteratively. The primary effectiveness endpoint will also be analyzed using Kaplan Meier methods. Per FDA's request, a sensitivity analysis was added to compare the primary effectiveness by randomization (i.e., to compare the DCD Heart Possible Population vs. the SOC Heart Only Population).

The protocol defines the secondary effectiveness endpoint (DCD donor heart utilization rate) as the number of eligible DCD donor hearts that met the warm ischemic time (WIT) limit (≤30 mins) and were instrumented on the OCS Heart System that meet the acceptance criteria for transplantation after OCS Heart preservation divided by the total number of eligible DCD donor hearts that met the warm ischemic time limit above and were instrumented on the OCS Heart System (i.e., based on the OCS Heart Population). It is clarified in the SAP that this is the primary analysis of the secondary effectiveness endpoint. The utilization rate based on the modified OCS (mOCS) Heart Population is added in the SAP, defined as the number of DCD hearts that were successfully transplanted after preservation and assessment on the OCS divided by the total number of DCD donor hearts that were instrumented on the OCS.

The protocol defines post-transplant mechanical circulatory support (MCS) as LVAD, RVAD, and BiVAD. The list of MCS was updated to also include ECMO, TAH, and IABP. For the study endpoint of use of post-transplant MCS for > 72 hours immediately post-transplant, it was clarified that only post-transplant MCS that is initiated within the initial 24 hours (T24 visit) post-OR discharge with an implant duration of greater than 72 hours will be considered to meet this study endpoint. This was proposed to avoid double counting IABP that was inserted pre-transplant and stayed for 1-2 days until the patient clotting factors are stabilized post-transplant.

Pre-transplant IABP (regardless of indication) that is removed per standard of care a couple of days post-transplant will be excluded from any post-transplant MCS analysis. Pre-transplant IABP that is maintained during transplantation and restarted for post-transplant cardiac support, and any IABP placed post-transplantation will be considered as newly placed IABP and included in the MCS endpoint analysis. Additionally, the newly placed IABP will be summarized by its indication as shown in the Figure 2 below. These IABP categories and indications will be adjudicated by the CEC.

Figure 2. Inclusion of IABP in Post-transplant (Post-Tx) MCS Analysis



Primary Graft Dysfunction (PGD) data for SOC patients (SOC1+ SOC2) will be collected from the investigational sites and adjudicated by CEC according to the ISHLT criteria. The ISHLT PGD will be summarized for the SOC patients based on CEC adjudication and will be compared to the DCD heart transplanted patients using descriptive statistics.

The patient survival, graft survival and hospital discharge information will be collected for SOC patients from the UNOS/OPTN database. The graft survival of SOC patients will be analyzed following CEC adjudication. Per the UNOS/OPTN Heart TRR form, graft failure includes heart re-transplantation and the cardiac-graft related death. Deaths that are a result of some other factor unrelated to graft failure are not included in this endpoint.

Number of HGRSAEs will be calculated for SOC patients by combining ISHLT moderate or severe PGD and primary graft failure requiring re-transplantation within the first 30 days post-transplant. HGRSAEs for the SOC patients will be compared to the DCD heart transplanted patients.

In summary, other endpoints were added, including:

- Patient and graft survival at 30 days post-transplant for SOC patients.
- Patient and graft survival at 30 days or initial hospital discharge, if later than 30 days for SOC patients.
- ISHLT moderate-severe PGD (left or right ventricle) (not including rejection or cardiac tamponade) within 24 hours according to ISHLT consensus manuscript (as defined in Appendix 1 of the protocol) for both OCS and SOC patients.
- ISHLT severe PGD (left or right ventricle) (not including rejection or cardiac tamponade) within 24 hours according to ISHLT consensus manuscript (as defined in Appendix 1 of the protocol) for SOC patients.
- HGRSAEs for SOC patients, consisting of ISHLT moderate or severe PGD and primary graft failure requiring re-transplantation within 30 days post-transplant.
- Kaplan-Meier estimated patient and graft survival at 30, 180, and 365 days post-transplant for both OCS and SOC patients.

A site poolability analysis for the primary efficacy endpoint was added for the DCD/SOC Heart Transplanted Recipient Population and for the DCD-mITT/SOC m-ITT Heart Transplanted Recipient Population.

Subgroup analyses of survival and severe ISHLT PGD endpoints were added for the DCD Heart/DCD-mITT Population. The subgroups will be based on WIT (0 - 20 minutes vs. >20 - 30 minutes vs. >30 minutes).

4.0 EFFECTIVENESS AND SAFETY ENDPOINTS

All effectiveness and safety endpoints based on primary heart graft dysfunction (PGD) results and the patient graft failure will use the Clinical Events Committee (CEC) adjudicated results.

4.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is patient survival assessed at the six months post-transplant follow-up visit (nominal visit).

4.2 Secondary Effectiveness Endpoint

The primary analysis of the secondary effectiveness endpoint is the utilization rate based on the OCS Heart Population, which is defined as the number of eligible DCD donor hearts that met the warm ischemic time (WIT) limit (≤30 mins) and were instrumented on the OCS Heart System that meet the acceptance criteria for transplantation after OCS Heart preservation divided by the total number of eligible DCD donor hearts that met the warm ischemic time limit above and were instrumented on the OCS Heart System.

The utilization rate based on the modified OCS (mOCS) Heart Population is defined as the number of DCD hearts that were successfully transplanted after preservation and assessment on the OCS divided by total number of DCD donor hearts that were instrumented on the OCS.

4.3 Other Endpoints

Other endpoints collected for the DCD heart transplanted subjects only include:

- Use of post-transplant MCS (including LVAD, RVAD, BiVAD, ECMO, TAH, IABP) for > 72 hours immediately post-transplant (i.e., use initiated within 24 hours after OR discharge).

Other endpoints collected for both the DCD heart transplanted recipients and the SOC heart transplanted recipients (SOC1+SOC2) are as follows:

- 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.
- ISHLT moderate-severe PGD (left or right ventricle) (not including rejection or cardiac tamponade) within 24 hours according to ISHLT consensus manuscript (as defined in Appendix 1 of the protocol) for both OCS and SOC patients.
- ISHLT Severe PGD (left or right ventricle) (not including rejection or cardiac tamponade) within 24 hours according to ISHLT consensus manuscript (as defined in Appendix 1 of the protocol).
- Patient survival assessed at the 12 months post-transplant follow-up visit.
- Patient and graft survival at 30, 180, and 365 days post-transplant estimated by Kaplan Meier method.

4.4 Safety Endpoint

The safety endpoint is defined as the incidence of Heart Graft-Related Serious Adverse Events (HGRSAEs) in the first 30 days post-heart transplantation, defined as:

- Moderate or Severe heart PGD (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript (as defined in Appendix 1 of the protocol).
- Primary graft failure requiring re-transplantation.

This endpoint is collected for both the DCD heart transplanted recipients and the SOC heart transplanted recipients (SOC1+SOC2).

5.0 STATISTICAL CONSIDERATIONS

5.1 General Methodology

All statistical analyses will be performed using SAS® Version 9.4. For the most part, the summary tables will be by analysis population [DCD Heart Transplanted Recipient Population, DCD modified-Intent-to-Treat Heart Transplanted Recipient Population, SOC Heart Transplanted Recipient Population (SOC1, SOC2, and Total) and/or SOC modified-Intent-to-Treat Heart Transplanted Recipient Population (SOC1, SOC2, and Total)]. The summaries of the secondary effectiveness endpoint (the utilization rate), and device malfunction will be produced for the OCS Heart Population and the modified OCS Heart Population.

Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation (SD), minimum and maximum. Categorical variables will be summarized using frequencies and percentages.

5.2 Adjustments for Covariates

The analysis of the primary effectiveness endpoint will be performed using a linear probability model with terms for treatment and the known donor and recipient risk factors for mortality listed in Section 12.1.

5.3 Handling of Dropouts and Missing Data

No imputation of missing data for trial subjects will be performed for any effectiveness or safety outcome.

An AE will be considered treatment emergent unless it can be unequivocally determined (from the partial onset date and/or a partial or complete stop date) that the event occurred prior to transplantation.

For duration of ICU stay calculation, the date time of the clinical order of discharge will be used. If the clinical order of discharge date is not available, the actual discharge date will be used. Missing ICU admission time will be imputed as 00:00, and missing ICU discharge time will be imputed as 23:59. If the imputed clinical order of discharge date time is after the actual discharge, the actual discharge date time will be used for calculation.

For duration of post-transplant MCS calculation, missing support start time will be imputed as 00:00, and missing support end time will be imputed as 23:59. If the imputed MCS start time is before the OR discharge, the OR discharge time will be used as the starting point for the duration calculation.

5.4 Interim Analyses and Data Monitoring

No interim analyses will be performed. The study database will have a database lock for the Premarket Approval (PMA) when all transplanted subjects either complete the Month 6 visit assessments or discontinue the study prematurely. Once all DCD patients complete Month 12 visit or discontinue the study, the additional data cut will be provided for FDA submission.

5.5 Multicenter Studies

Subjects will be recruited from up to 25 sites. The effect of site and the treatment by site interaction will be tested via logistic regression. The Wald Type III p-value for site and the treatment by site interaction term will be presented.

5.6 Multiple Comparisons / Multiplicity

No adjustments for multiple comparisons/multiplicity will be made.

5.7 Examination of Subgroups

Subgroup analyses of the survival and PGD endpoints for the DCD /DCD-mITT Heart Transplanted Recipient Population will be performed based on the following WIT subgroups: 0 to 20 minutes; >20 to 30 minutes; and >30 minutes.

6.0 ANALYSIS POPULATIONS

The ***DCD Heart Transplanted Recipient Population*** will consist of all eligible recipients who were randomized and transplanted with an eligible DCD donor heart that met the warm ischemic time (WIT) limit (WIT ≤ 30 mins), preserved on OCS and met all transplantability criteria. Recipients transplanted with a pediatric donor heart will be excluded from this analysis population as these donor hearts do not meet eligibility criteria for the trial.

WIT is defined as time from when mean systolic blood pressure (SBP) is < 50 mmHg or peripheral saturation < 70%, whichever occurs first, to aortic cross-clamp and administration of cold cardioplegia in the donor.

The ***DCD modified Intent-to-Treat (DCD-mITT) Heart Transplanted Recipient Population*** will include all recipients who were randomized and transplanted with a DCD donor heart that was instrumented on the OCS Heart System.

The ***SOC Heart Transplanted Recipient Population*** will consist of all recipients who received a standard criteria donor heart (***SOC1 + SOC2*** as defined in **Section 3.2**), excluding recipients transplanted with a pediatric donor heart.

The ***SOC modified Intent-to-Treat (SOC-mITT) Heart Transplanted Recipient Population*** will consist of all recipients who received a standard criteria donor heart (***SOC1 + SOC2***).

The ***OCS Heart Population*** will consist of all randomized DCD donor hearts that were instrumented on the OCS Heart System without protocol deviations. Donor hearts with warm ischemic time > 30 mins or from pediatric donors will be excluded. The primary analysis of utilization rate will be based on the OCS Heart Population.

The ***modified OCS (mOCS) Heart Population*** will consist of all randomized DCD donor hearts that were instrumented on the OCS Heart System. The DCD donor heart utilization rate will also be calculated based on this modified OCS Heart Population.

The ***DCD Heart Possible Population*** will consist of all eligible recipients who are randomized to the DCD Heart Possible group and receive either a DCD heart preserved on OCS or an SOC donor heart.

The ***SOC Heart Only Population*** will consist of all eligible recipients who are randomized to the SOC Heart Only group and receive a SOC heart.

After completing enrollment there were 6 cases in which a SOC donor heart was transplanted without randomization. Since those 6 patients were transplanted without randomization, they will be excluded from any analysis populations.

7.0 SUBJECT AND DONOR HEART DISPOSITION

The number of applicable recipients will be presented for each of the following categories:

- Signing the informed consent
- Transplanted without randomization
- Randomized to DCD Heart Possible arm
- Randomized to SOC Heart Only arm
- Randomized but not transplanted, subject disposition
- Randomized and transplanted with DCD hearts (DCD-mITT population)
- Randomized and transplanted with SOC hearts (SOC-mITT population)
- Transplanted with DCD heart per-protocol (DCD Heart Transplant Recipient Population)
- Transplanted with SOC heart per-protocol (SOC Heart Transplant Recipient Population)

The number and percentage of SOC heart transplanted recipients (SOC1, SOC2, and Total) and DCD heart transplanted recipients who completed the study, who died on study, who discontinued from the study early, both overall and by time period (before day 30, between day 30 and 6 months, and between 6 months and 12 months), and the reason for early discontinuation will also be presented. Re-transplanted patients will be considered as discontinued the study at the time of re-transplantation.

Donor heart disposition and acceptance details will be summarized for all donor hearts in the database using frequencies and percentages for the following categories:

- All donor hearts screened in the database
- Donor hearts transplanted without randomization
- Donor hearts by randomized recipient and by organ type (DBD or DCD)
- Donor hearts dry-run by recipient randomization
- Donor hearts instrumented on the OCS Heart System (mOCS Heart Population)
- Donor hearts instrumented on the OCS Heart System without protocol deviations (OCS Heart Population)
- Donor hearts instrumented on the OCS Heart System that did not meet the WIT limit or were pediatric donors

8.0 PROTOCOL DEVIATIONS AND VIOLATIONS

Protocol deviations will be summarized for the DCD-mITT Heart Transplanted Recipient Population and the SOC-mITT Heart Transplanted Recipient Population (SOC1, SOC2, and Total) by type of deviation and overall using counts and percentages.

Prior to the database lock, protocol violations will be identified and documented based on a review of potential protocol violations. The protocol violations include, but are not limited to, subjects who did not meet key inclusion/exclusion criteria or transplantability criteria for OCS group, and pediatric donor for SOC group. Patients with at least one protocol violation will be excluded from the DCD and SOC Heart Transplanted Recipient Populations but will be included in DCD-/SOC-mITT populations.

9.0 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Recipient and donor demographic and baseline characteristics will be summarized for the DCD-mITT Heart Transplanted Recipient Population, the DCD Heart Transplanted Recipient Population, the SOC-mITT Heart Transplanted Recipient Population, and the SOC Heart Transplanted Recipient Population. Frequencies and percentages will be presented for categorical variables, and descriptive statistics will be presented for continuous variables.

Recipient non-cardiac medical history at screening will be summarized for the SOC Heart Transplanted Recipient Population, the SOC-mITT Heart Transplanted Recipient Population, the DCD Heart Transplanted Recipient Population, and the DCD-mITT Heart Transplanted Recipient Population using descriptive statistics for continuous variables and frequencies and percentages for categorical variables.

Donor medical history will be summarized for the SOC Heart Transplanted Recipient Population, the SOC-mITT Heart Transplanted Recipient Population, the DCD Heart Transplanted Recipient Population, and the DCD-mITT Heart Transplanted Recipient Population using frequencies and percentages.

Donor heart procurement data will be summarized for the DCD Heart Transplanted Recipient Population and the DCD-mITT Heart Transplanted Recipient Population using frequencies and percentages. Total number of days since recipient was consented until transplanted and total number of days since recipient was placed on waiting list will be summarized for DCD and SOC patients.

10.0 OCS PRESERVATION CHARACTERISTICS

OCS perfusion time and ischemic time will be summarized using descriptive statistics for the DCD Heart Transplanted Recipient Population, the DCD-mITT Heart Transplanted Recipient Population, and the turn-down hearts. Donor heart chemistry data on OCS instrumentation will be summarized by time point (initial OCS instrumentation, and final OCS instrumentation) using descriptive statistics for the DCD Heart Transplanted Recipient Population and the DCD-mITT Heart Transplanted Recipient Population and turn-down hearts.

Device malfunction data will be summarized using frequencies and percentages.

11.0 TRANSPLANT CHARACTERISTICS

Summaries of transplant details for the DCD and DCD-mITT Heart Transplanted Recipient Populations will be presented, using descriptive statistics for continuous variables and frequencies and percentages for categorical variables.

12.0 EFFECTIVENESS ANALYSES

All PGD based effectiveness endpoints will be based on the recipient CEC adjudicated primary graft surveillance data.

12.1 Primary Effectiveness Endpoint Analyses

The primary effectiveness endpoint is a comparison of survival at the six months post-transplant visit for DCD heart transplanted recipients and standard criteria heart transplanted recipients (SOC1 + SOC2), adjusting for differences in known risk factors. It will be calculated for both the DCD/SOC Heart Transplanted Recipient Populations and the DCD/SOC-mITT Heart Transplanted Recipient Populations, with the comparison of the DCD Heart Transplanted Recipient Population vs. the SOC Heart Transplanted Recipient Population considered the primary analysis. This is a non-inferiority study.

We will adjust for the known donor and recipient risk factors for mortality shown in the list below:

Donor Variables:

- Donor age ≥ 55 years
- Ischemic Time ≥ 4 hours
- Gender mismatch (female donor to male recipient).

Recipient Variables:

- Recipient age ≥ 65 years
- MCS (including LVAD, RVAD, BiVAD, ECMO, TAH, or IABP) prior to transplant
- Mechanical ventilation at time of transplant

The null and alternative hypotheses for the primary endpoint are as follows:

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

vs.

H_1: $p_{SOC} - p_{DCD} < 0.20$

where p_{DCD} and p_{SOC} represent the true survival proportions at the six months follow-up visit for DCD and SOC heart transplant patients, respectively.

The primary analysis of this endpoint will be performed using a linear probability model, with the following terms in the model: (1) treatment; and (2) the known donor and recipient risk factors listed above. Variables that make the model fail to converge (e.g., due to quasi-complete separation of datapoints) will be dropped from the model. The p-value for the test of the null hypothesis will be obtained based on a statistic for the difference (SOC - DCD) in least squares mean proportions for each treatment minus the non-inferiority margin of 0.20 all divided by the standard error of the difference in the least squares mean proportions and assuming an approximate normal distribution. The test will be conducted at the one-sided 0.05 level of significance. Additionally, this endpoint will be summarized by treatment group using counts

and percentages, and an exact (Clopper-Pearson) 95% confidence interval for the percentages will be presented.

Generalized SAS code to implement this analysis is given below:

```
ods output diffs=diffs lsmeans=lsmeans;
proc genmod descending;
    class trt01a (ref='DCD');
    model survival=trt01a riskfactors / dist=binomial link=identity;
   lsmeans trt01a / diff cl alpha=0.1;
run;

data diffs;
  set diffs;
  pvalue=put(probnorm((estimate - 0.20)/stderr), 6.4));
run;
```

Per FDA's request, a sensitivity analysis will be performed to compare the DCD Heart Possible Population vs the SOC Only Population, i.e. (DCD + SOC2) vs SOC1. Also at FDA's request, an additional sensitivity analysis will repeat the primary effectiveness analysis with the same non-inferiority margin but without adjustment for covariates. Finally, assuming the primary analysis results demonstrate non-inferiority of OCS to SOC, a tipping point analysis (without risk factor adjustment) will be performed using the Wald method, in which SOC subjects categorized as having an unsuccessful 6-month survival outcome will be iteratively imputed as having a successful survival outcome. The "tipping point" is the number of SOC subjects needed to be imputed as having successful outcomes in order to no longer reject the null hypothesis of inferiority.

An additional analysis of the primary endpoint will evaluate pooling by recipient investigational site. This analysis will be performed on observed data for both the DCD/SOC Heart Transplanted Recipient Populations and the DCD/SOC-mITT Heart Transplanted Recipient Populations. A logistic regression model will be fit with all terms included in the primary effectiveness analysis, site, and the interaction of site with treatment. The p-values for site and the treatment by site interaction term in the model will be presented, with statistical significance defined at the $\alpha = 0.15$ level. Sites with ≤ 10 subjects will be pooled for this analysis.

12.2 Secondary Effectiveness Endpoint Analyses

The primary analysis of the secondary effectiveness endpoint is the utilization rate based on the OCS Heart Population, defined in Section 4.2. This endpoint will be summarized for the OCS Heart Population using counts and percentages and an exact (Clopper-Pearson) 95% confidence interval for the true percentage based on the binomial distribution. It will also be summarized for the modified OCS Heart Population, defined as the number of DCD hearts that were successfully transplanted after preservation and assessment on the OCS divided by the total number of DCD donor hearts that were instrumented on the OCS.

12.3 Other Effectiveness Endpoints Analyses

Other endpoints collected for the DCD and DCD-mITT Heart Transplanted Recipient Populations include:

- Use of post-transplant MCS (includes LVAD, RVAD, BiVAD, ECMO, TAH, or IABP) for > 72 hours immediately post-transplant. To clarify, pre-transplant IABP (regardless of indication) that is removed per standard of care a couple of days post-transplant will be excluded from any post-transplant MCS analysis. The pre-transplant IABP that is maintained during transplantation and restarted for post-transplant cardiac support, and the IABP placed post-transplantation will be considered as newly placed IABP. Only the post-transplant MCS initiated within the initial 24 hours (T24 visit) post-transplant with a duration of use greater than 72 hours will be considered to meet this study endpoint. In cases where a recipient received more than one type of post-transplant support, the support type with the longest continuous duration will be used.

Other endpoints collected for both the DCD heart transplanted recipients and the SOC heart transplanted recipients (SOC1+SOC2) include:

- 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
- Moderate-severe PGD (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript (as defined in Appendix 1 of the protocol) within 24 hours post-transplant
- Severe PGD (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript (as defined in Appendix 1 of the protocol) within 24 hours post-transplant
- Patient survival assessed at the 12 months post-transplant follow-up visit
- Patient and graft survival at 30, 180, and 365 days post-transplant estimated by Kaplan Meier method

Each endpoint, except Kaplan-Meier estimates, will be summarized using counts and percentages and an exact (Clopper-Pearson) 95% confidence interval for the true percentage based on the binomial distribution.

Kaplan-Meier estimates for patient survival and graft survival (graft failure includes heart re-transplant and cardiac graft-related death) probabilities will be calculated for the SOC Heart Transplanted Recipient Population, the SOC-mITT Heart Transplanted Recipient Population, the DCD Heart Transplanted Recipient Population, and the DCD-mITT Heart Transplanted Recipient Population for the following time points: Day 30, Month 6, and Month 12. Of note, the Kaplan-Meier estimates will consider time as a continuous variable measured in days. The Month 6 and Month 12 timepoints will be considered to be 180 and 365 days post-transplantation, respectively. Re-transplanted patients will be censored at the day of re-transplantation. The estimated difference in survival probability (SOC – DCD) and its 90% confidence interval will also be presented at each of the three time points.

13.0 SAFETY ANALYSES

Heart Graft-related Serious Adverse Events (HGRSAEs) will be collected within the first 30 days post-transplant for all subjects.

HGRSAEs are defined as the following adverse events (at most one per type): Moderate or Severe heart PGD (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript and primary graft failure requiring re-transplantation.

The number of HGRSAEs per subject will be summarized using descriptive statistics for the DCD/SOC Heart Transplanted Recipient Populations and for the DCD-mITT/SOC-mITT Heart Transplanted Recipient Populations.

Serious Adverse Events (SAEs) will be collected within the first 30 days post-transplant for the DCD heart transplant recipients only. SAEs will be summarized for the DCD and DCD mITT Heart Transplanted Recipient Populations. The numbers and percentages of subjects experiencing at least one treatment- emergent SAE in the following categories will be tabulated: at least one heart graft-related SAE, at least one severe SAE, at least one severe heart graft-related SAE, at least one unanticipated SAE, at least one unanticipated HGRSAE.

SAEs will be summarized by MedDRA system organ class and preferred term, and HGRSAEs will be summarized by event type. They will also be tabulated using counts and percentages by relationship with the device (Definite, Probable, Possible, Unlikely, and Unrelated) and by severity. For the subject counts, if the same event occurs for a subject on multiple occasions, the event will be categorized according to the closest relationship and highest severity rating for the event in that subject.

14.0 OTHER ANALYSES

Use of post-transplant MCS (includes LVAD, RVAD, BiVAD, ECMO, TAH, or IABP) will be summarized. Pre-transplant IABP (regardless of indication) that is removed per standard of care a couple of days post-transplant will be excluded from any post-transplant MCS analysis. Pre-transplant IABP that is maintained during transplantation and restarted for post-transplant cardiac support, and the IABP placed post-transplantation will be considered as newly placed IABP. Frequencies and percentages of patients with post-transplant MCS will be summarized overall and by support type. Descriptive statistics for duration of support will be provided for each type. Post-transplant IABP will also be tabulated by indications, including per center specific protocol - prophylactic, for cardiac support (graft dysfunctions not meeting the PGD criteria), and for PGD. IABP and indications will be summarized by CEC adjudication.

Recipient post-transplant ICU stay(s) will be summarized using descriptive statistics for the initial ICU stay duration to clinical order of discharge and the re-admission ICU stay duration from ICU re-admission to clinical order of re-admission discharge, and using frequencies and percentages for whether the recipient was readmitted in the ICU.

Post-transplant hospitalization(s) will be summarized using descriptive statistics for the initial hospital stay duration and the re-hospitalization stay duration and frequencies and percentages for whether the recipient was re-hospitalized.

Primary graft dysfunction surveillance data through 24 hours post-transplant will be summarized using frequencies and percentages for both DCD and SOC groups.

Post-transplant invasive hemodynamics, inotropic suport and echocardiogram data will be listed.

The above analyses will be performed for the DCD Heart Transplanted Recipient Population and DCD-mITT Heart Transplanted Recipient Population. The above analyses will be done for the SOC Heart Transplanted Recipient Population and SOC modified Intent-to-Treat (SOC-mITT) Heart Transplanted Recipient Population, only if explicitly stated.

15.0 REFERENCES

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APPENDIX A: TABLE SHELLS