Advisory Committee Briefing Materials:
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TransMedics® Organ Care System™ (OCS™) Liver System

(b)(4)

Sponsor Executive Summary

Gastroenterology and Urology Devices Advisory Panel

July 14, 2021

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1. OVERVIEW OF CLINICAL EVIDENCE SUPPORTING THE OCS LIVER SYSTEM

1.1. Introduction

This document is intended to present to the Advisory Panel the following information:

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

Section 1 of this document is designed to provide the high-level summary of all the clinical evidence and associated conclusions in support of the approval of this PMA for the OCS Liver System. The primary data set supporting this PMA is the PROTECT trial, a randomized, controlled, multicenter U.S. clinical trial comparing post-transplant outcomes for recipients of donor livers preserved and assessed on the OCS Liver System to those of recipients of donor livers preserved on standard of care ischemic cold storage. The primary and secondary effectiveness endpoints were met, and the OCS Liver System demonstrated superiority to the cold storage control in the reduction of Early Allograft Dysfunction (EAD). In addition, the use of the OCS Liver System was associated with a clinically significant reduction of ischemic biliary complications at 6 and 12 months. The safety endpoint was also met, and there were no safety concerns identified for the OCS Liver System.

This Overview also outlines TransMedics' position on the key areas of concerns raised by FDA in their panel material, which focused on:

- The OCS Liver System's assessment capabilities;
- Perceived missing data (from recipient screen failures) and appropriateness of an ITT analysis;
- Statistical issues including multiplicity adjustment;
- PROTECT trial randomization process and its potential impact on the trial results;
- The occurrence of 3 DCD liver allograft turndowns after OCS Liver assessment, and whether they pose a potential risk to the intended recipient;
- The definition of EAD and the clinical value of the significant reduction of EAD in the OCS arm that was demonstrated in the PROTECT Trial;
- The 3 device malfunctions that were reported and whether they pose a potential risk to the intended recipients;
- Clinical outcomes of the DCD liver subgroup in the PROTECT trial;
- Overall clinical benefit and value of the OCS Liver System

1.2. Proposed Indications for Use for the OCS Liver System

In this PMA, TransMedics is seeking approval for the following indications for use for the OCS Liver System:

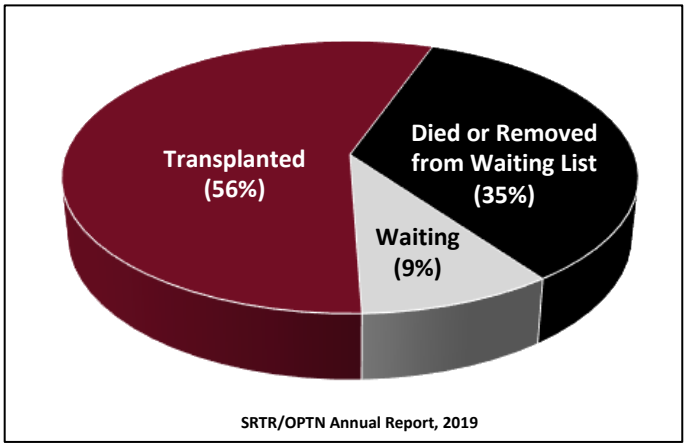
> ***The TransMedics® Organ Care System (OCS™) Liver is a portable extracorporeal liver perfusion and monitoring system indicated for the resuscitation, preservation, and assessment of liver allografts from donors after brain death (DBD) or liver allografts from donors after circulatory death (DCD) ≤55 years old in a near-physiologic, normothermic and functioning state intended for a potential transplant recipient.***

1.3. Clinical Background

Today, liver transplantation is universally accepted as the only curative treatment option for end-stage liver disease secondary to acute fulminant hepatic failure, several forms of liver cancers, and metabolic disorders. Today, there are several clinical challenges facing liver transplant therapy:

- ***Shortage of donor liver allografts*** **-** The availability of donor liver allografts has not kept pace with the demand[1]. The utilization of available DBD donor livers and the utilization of DCD donor livers are severely restricted by the limitations of cold ischemic storage of donor livers;
- ***High waiting list mortality of end-stage liver patients awaiting liver transplantation due to the shortage of supply of suitable donor livers for transplantation.*** The 2019 SRTR/OPTN Annual Report shows 35% mortality of the liver transplant waiting list in the US. (Figure 1 below).

Figure 1: Three-year outcomes on Waiting List for Liver Transplantation



- ***High post-transplant complications in the form of Early Allograft Dysfunction (EAD) and Ischemic Biliary Complications (IBC)*** – Both are associated with short- and long-term graft failure and increased morbidity (Olthoff, et al., 2010; Hudcova, et al., 2017);

[1] This background and summary are focused on organs from deceased donors, which make up the majority of liver transplants today, and are appropriate for use of the OCS Liver System. The number of living donor transplants is relatively small: UNOS reported 8,415 deceased donor liver transplants for 2020, and 491 living donor liver transplants during this same year.

- ***Lastly, the donor pool is increasingly made up of higher risk donors (older age, complex medical history, etc.)*** – which impacts recipient outcomes and further complicates the clinical acceptance of these challenging donors for transplantation (MacConmara, et al., 2020).

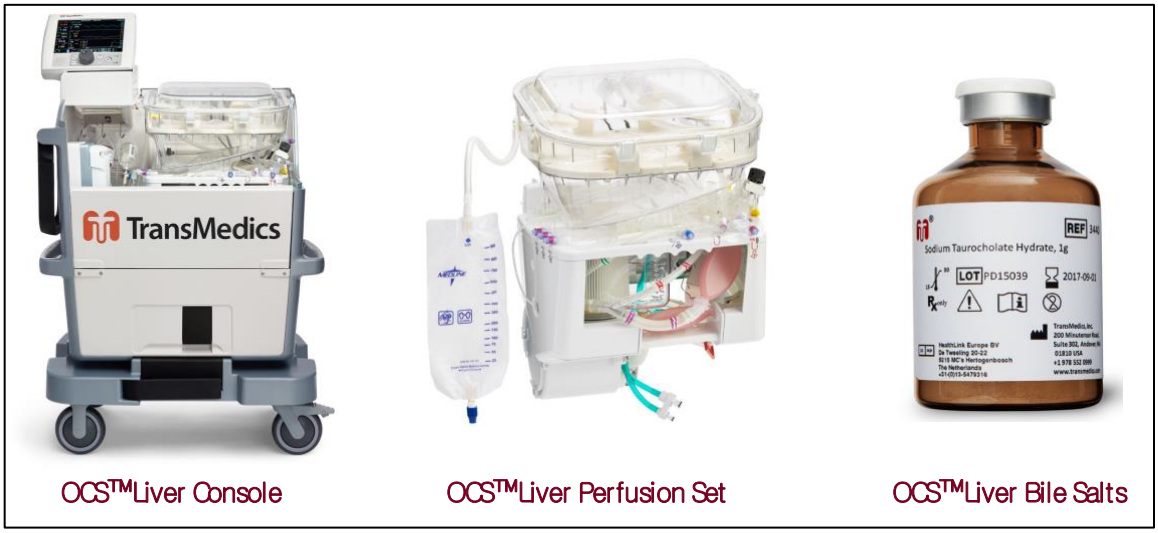
The primary driver of the above clinical challenges are the significant limitations of ischemic cold storage which has been used for 40+ years to preserve donor livers. These limitations hamper the clinicians' ability to maximize donor liver utilization for transplants and are correlated with negative post-transplant clinical outcomes. These limitations include:

- Severe time-dependent ischemic injury to the donor liver, which correlates with the development of post-transplant complications like early allograft dysfunction (EAD) and ischemic biliary complications, which are associated with a significant risk of graft loss and increased risk of morbidity and mortality. Importantly, this limits the geographical time/distance for procuring donor livers for transplantation.
- No capability to optimize/resuscitate the liver allograft from the non-physiologic sub-optimal environment of organ donation from brain dead donors (DBD) or donors after circulatory death (DCD).
- No ability to assess liver allograft viability for transplantation after it has been removed from the donor body.

The OCS Liver System was designed to overcome the above limitations of ischemic cold storage. The OCS maintains the donor liver in a non-ischemic, metabolically active and functioning state (producing bile) by perfusing the liver with a warm, oxygenated, and nutrient-enriched blood-based perfusion solution. The OCS enables metabolic resuscitation/optimization of the donor liver from the challenging environment of brain death and DCD donation, by maximizing substrate delivery, replenishing key hormones and administration of vasodilators and broad-spectrum antibiotics, etc. The OCS Liver System is intended to significantly reduce ischemia and reperfusion injuries on the donor livers and enable metabolic and functional assessment of donor livers to assess their suitability for transplantation.

There are 3 main components of the OCS Liver System are shown in Figure 2 below.

Figure 2: OCS Liver System



The OCS Liver System was developed to enable the following clinical advantages to liver transplantation:

- Reduction of ischemia and reperfusion injuries on the donor livers during preservation, leading to improvement in post-transplant clinical outcomes and the potential elimination of the significant logistical and geographical barriers to liver transplantation that currently exist with cold storage preservation.
- Resuscitation of donor livers ex-vivo from the challenging environment of DBD or DCD organ donation by optimizing oxygen, substrates, hormones, and pharmacological substances to maximize the opportunity of utilizing donor livers for transplants.
- Ex-vivo assessment of donor liver metabolic and functional state including standard liver enzyme tests, bile production, lactate metabolism, as well as hemodynamics. These assessments provide prospective objective clinical data points to enable the transplanting surgeons to gain more confidence on the suitability of the donor liver for transplantation. Importantly, they minimize the risk of transplanting questionable donor livers into recipients. This assessment capability is paramount for DCD donor livers which have been subjected to a period of warm ischemic damage prior to procurement.

1.4. OCS Liver Assessment Capabilities

The FDA raised a concern about OCS Liver's assessment capabilities and whether the parameters are validated to assess donor liver function. First, TransMedics would like to clarify that the OCS perfusion chemistry levels are the same clinically validated tests used in everyday assessment of liver function both in the donor and in recipients post-transplant. Specifically, OCS livers were assessed using liver enzymes (AST and ALT) and lactate levels as well as bile production. Bile production is the hallmark of liver excretory function in humans. None of these tests are novel, nor were they used differently than their common use in clinical practice for several decades. Simply stated, the OCS Liver System provides the organ with a near-physiologic ex vivo environment that enables further assessment and monitoring of the organ by the same evaluations and assessment methods as clinicians currently use in the donor and recipient in vivo environments.

Second, we would like to point out that TransMedics provided the FDA with extensive animal testing results during the IDE review process that validated the relevance of these lab values, and we correlated them with liver histology. **Figure 3** below shows the lactate and AST levels during OCS perfusion in animal experiments during 12 hours of perfusion on the OCS. The lactate levels were very consistent with AST levels and followed the same trend. In addition, we assessed these same parameters (AST and lactate) in simulated transplant studies in the swine model and the same trend was seen (see **Figure 4** below). Both of these studies included extensive pathological assessment by a blinded liver transplant pathology core laboratory at (b) (6) . These studies demonstrated that these biochemical markers correlated with normal well-preserved hepatocyte and biliary structure pathology compared to elevated levels seen in the Control arm, which was associated with severe histopathological injury to the swine livers' hepatocytes and biliary tree. The preclinical animal studies are summarized in Appendix 2 of this document.

Figure 3: Pre-clinical OCS Perfusion Circulating Lactate and AST Levels over 12 Hours of OCS Liver Perfusion (N= 28 Animal Studies)

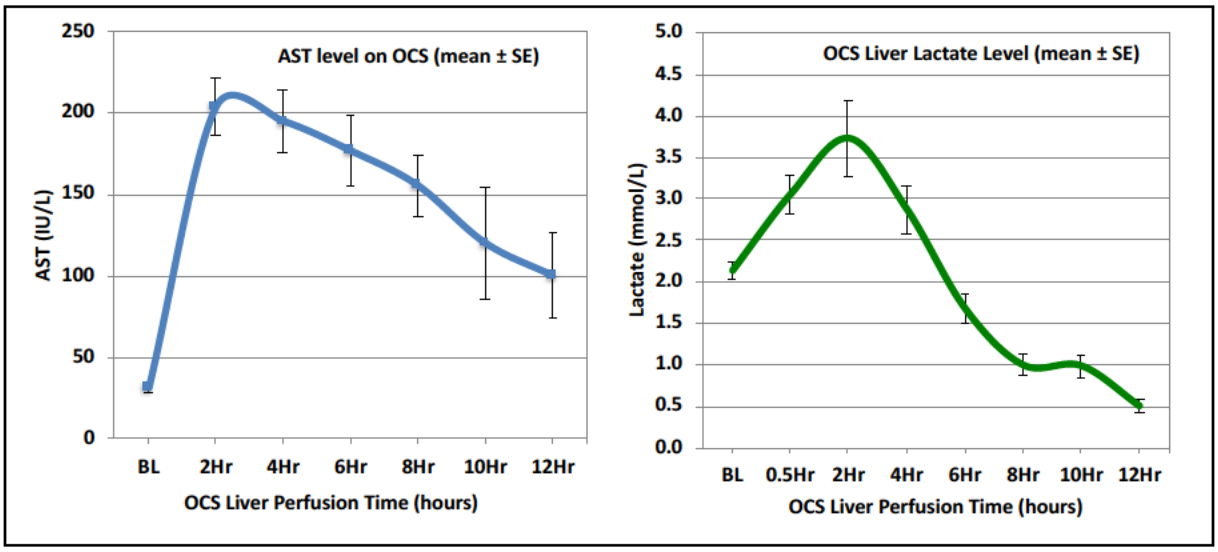
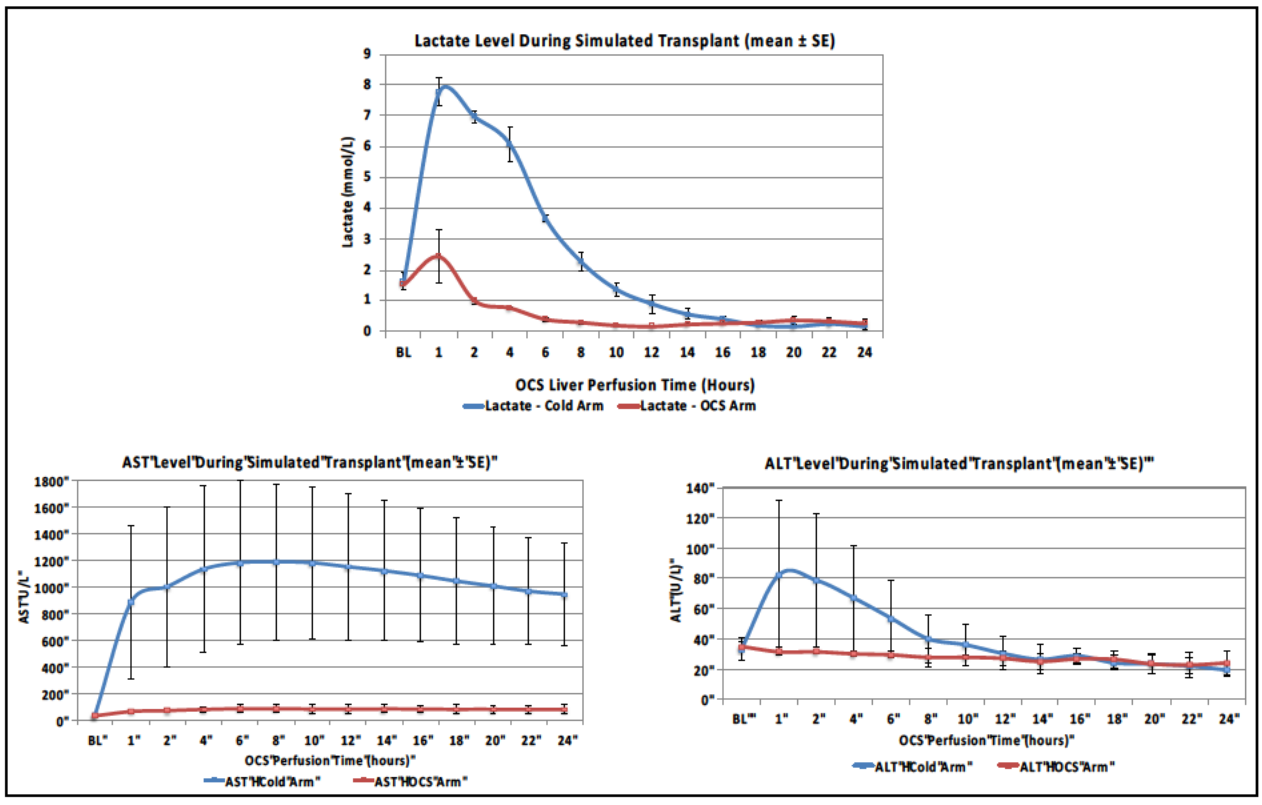


Figure 4: Simulated Transplant Animal Studies Results for Circulating Lactate and Liver Enzymes Post-Simulated Transplants 8-12 hours OCS Perfusion (N= 18 Animal Studies)



The above extensive pre-clinical testing laid the foundation for TransMedics to design the PROTECT trial to use lactate levels throughout OCS Liver perfusion (every ~2 hours), as well as liver enzymes at the beginning and end of OCS perfusion, and bile production to assess liver

function. The measurement of these parameters was pre-specified as the first secondary effectiveness endpoint to demonstrate the *ex vivo* assessment capabilities of the OCS Liver System.

1.5. Summary Overview & Results of OCS Liver PROTECT Trial

The OCS Liver PROTECT trial is the primary data set supporting this PMA application. It was a prospective, multi-center, randomized trial, with patients randomized 1:1 to the OCS Liver or Control (ischemic cold storage). The trial enrolled 300 patients at 20 U.S. liver transplant sites between January 2016 and October 2019. The clinical objective of the trial was to compare the safety and the effectiveness of the OCS Liver System vs. cold storage (Control) to preserve and assess donor livers intended for transplantation that may benefit from warm oxygenated perfusion compared to cold static storage from one or more of the following donor characteristics:

- Donor age ≥ 40 years old; or
- Expected total cross clamp/cold ischemic time ≥ 6 hours; or
- Donor after Cardiac Death (DCD donor) with age ≤ 55 years old; or
- Steatotic liver > 0% and ≤ 40% macrosteatosis at time of retrieval (based on retrieval biopsy readout (only if the donor liver was clinically suspected to be fatty by the retrieval surgeon at time of liver retrieval)).

1.5.1. Primary Effectiveness Endpoint

The Primary Effectiveness Endpoint is the incidence of Early liver Allograft Dysfunction (EAD). The FDA-approved PROTECT protocol pre-specified the definition of EAD as the presence of one or more of the following criteria:

- AST level > 2000 IU/L within the first 7 postoperative days;
- Bilirubin ≥ 10 mg/dL on postoperative day 7;
- INR ≥ 1.6 on postoperative day 7; or
- Primary non-functioning graft within the first 7 days (defined as irreversible graft dysfunction requiring emergency liver re-transplantation or death, in the absence of immunologic or surgical causes).

EAD for all patients was adjudicated by the independent Clinical Events Committee (CEC). See Section 6.2 of this summary for details on the CEC composition.

1.5.2. Secondary Effectiveness and OCS Donor Liver Assessment Endpoints

- OCS donor liver assessment during perfusion
- Patient survival at day 30 post-transplantation
- Patient survival at initial hospital discharge post liver transplantation.

1.5.3. Other Clinical Endpoints

- Evidence of ischemic biliary complications diagnosed at 6 and at 12 months

- Extent of reperfusion syndrome as assessed based on the rate of decrease of lactate
- Pathology sample score for liver tissue samples.
- Length of initial post-transplant ICU stay
- Length of initial post-transplant hospital stay

1.5.4. Safety Endpoint

The safety endpoint is the incidence of liver graft-related serious adverse events (LGRSAEs) in the first 30 days post liver transplantation, which are defined as:

- Primary non-function (defined as irreversible graft dysfunction, requiring emergency liver re-transplantation or death within the first 10 days, in the absence of immunologic or surgical causes);
- Ischemic biliary complications (ischemic biliary strictures, and non-anastomotic bile duct leaks);
- Vascular complications (liver graft-related coagulopathy, hepatic artery stenosis, hepatic artery thrombosis, and portal vein thrombosis); or
- Liver allograft infections (such as liver abscess, cholangitis, etc.).

Safety events for all patients were adjudicated by the CEC.

1.5.5. Analysis Populations

Per Protocol (PP) population: This was pre-specified as the primary analysis population. It consists of all randomized patients who were transplanted and had no major protocol violations, and for whom the donor liver received the complete preservation procedure as per the randomization assignment. In the PP analyses, patients were analyzed in the groups to which they were randomized. *The primary analysis of the primary and secondary effectiveness endpoints, and of other endpoints, are based on the PP population*.

The As Treated (AT) population: It consists of all treated patients, i.e., all patients who were transplanted in the trial with a donor liver preserved with either OCS or Control. In analyses based on this population, patients were analyzed as treated. *Analyses of safety endpoints are performed based on the AT population.*

The Modified Intent-to-Treat (mITT) population: It consists of all randomized patients who were transplanted in the trial. In the mITT Population, patients were analyzed as randomized. *The mITT analyses are the secondary analyses of effectiveness.*

Given the complexities of donor organ procurement for transplantation, and different logistical and clinical reasons that a donor organ may not be accepted for transplantation or eligibility, a traditional intent-to-treat analysis has never been used for designing any of TransMedics-designed randomized controlled organ preservation studies for the reasons outlined in the box below.

The FDA requested that TransMedics perform a post-hoc analysis of an Intent-to-Treat (ITT) population that includes 43 patients who were screen failures after randomization and were transplanted off-study and preserved using standard of care ischemic cold storage. ***TransMedics strongly believes that this post-hoc ITT population has several limitations that makes it inappropriate to interpret the PROTECT trial results beyond as a sensitivity analysis. These limitations are:***

- 43 patients in this analysis were screen failures who were *withdrawn and transplanted off-study with cold storage, making any clinical interpretation of comparative clinical outcomes of these 43 patients extremely difficult given that all were transplanted with ischemic cold storage and outside of the trial's control;*
- No data were collected on these patients' post-transplant outcomes in the PROTECT trial. Data was limited to patient and graft survival reported in the UNOS/SRTR national database. EAD data was imputed based on observed outcomes in PROTECT.

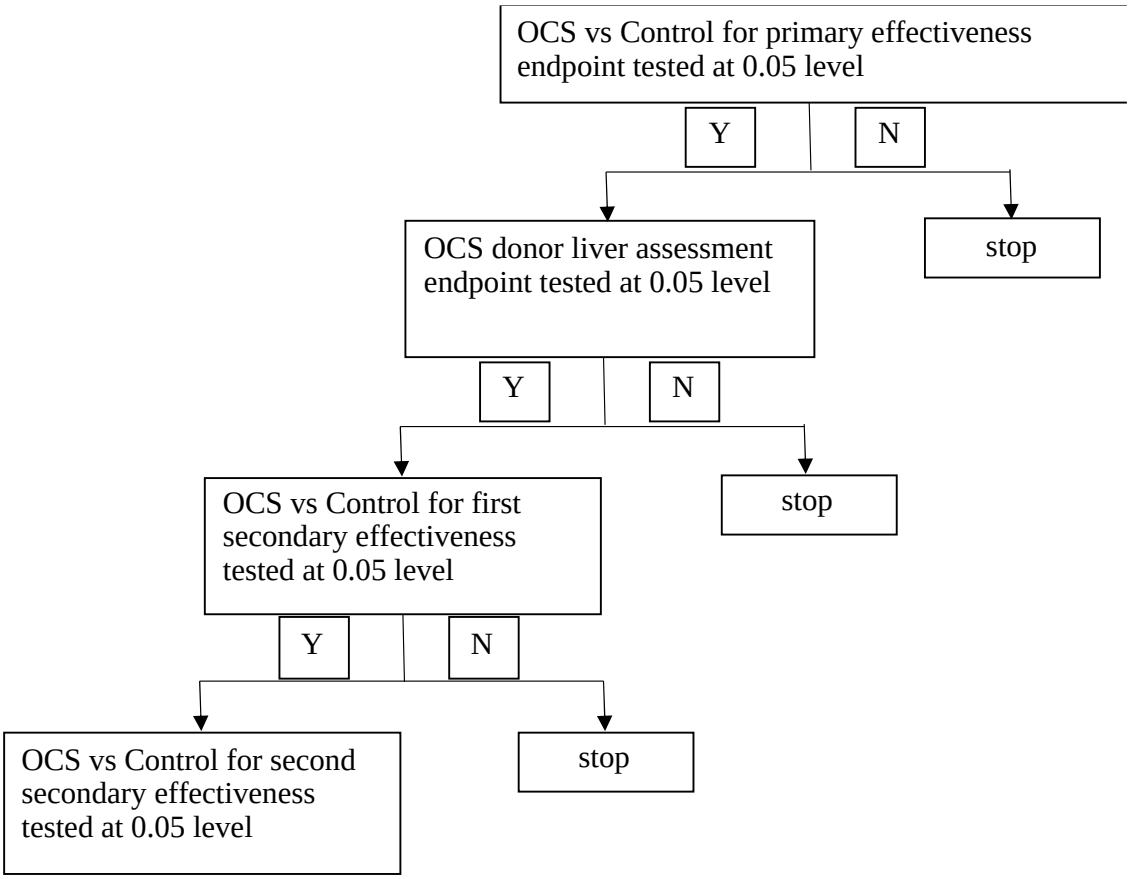
The FDA used this post-hoc, sensitivity analysis population of ITT to draw critical clinical conclusions on the results of the OCS Liver PROTECT trial. TransMedics respectfully believes this is an inappropriate analysis population to draw clinical conclusions based on the above significant limitations.

1.5.6. PROTECT Trial Statistical Analysis

The FDA raised a point in their FDA panel briefing material about multiplicity adjustment for the secondary effectiveness endpoints and also the safety endpoint for the PROTECT trial. TransMedics respectfully disagrees with the FDA comments based on the following facts:

- TransMedics provided the FDA with a flowchart of fixed sequence testing for the primary and secondary effectiveness endpoints and the FDA never questioned the sequence or asked for additional details of the testing sequence (see Figure 5). We followed an appropriate and reasonable approach to fixed sequence testing in that we first tested the primary endpoint for non-inferiority and then the first secondary endpoint (donor liver assessment) and two secondary endpoints for non-inferiority. After non-inferiority was shown for all the study points, superiority was tested for the primary and two secondary endpoints (30 days patient survival and hospital patient survival) following the same sequence. Superiority was shown for the primary endpoint first, allowing us to move on and to test for superiority in the secondary endpoint of 30-day survival. Since superiority was not shown in this endpoint, further superiority testing stopped, per the planned sequence.

Figure 5: Testing sequence for Non-inferiority and Superiority in PROTECT Trial



- The PROTECT trial protocol never prespecified a multiplicity adjustment for the Safety endpoint given that this endpoint is analyzed independently of the primary and secondary effectiveness endpoints and is based on a different analysis population.
- Importantly, in order to demonstrate that the device is safe and effective (i.e., for the study to be a success) in one pivotal trial, both effectiveness and safety endpoints would be expected to have been met. Since both endpoints needed to be met, there was no need to make an adjustment for multiplicity.

1.5.7. PROTECT Trial Randomization Process

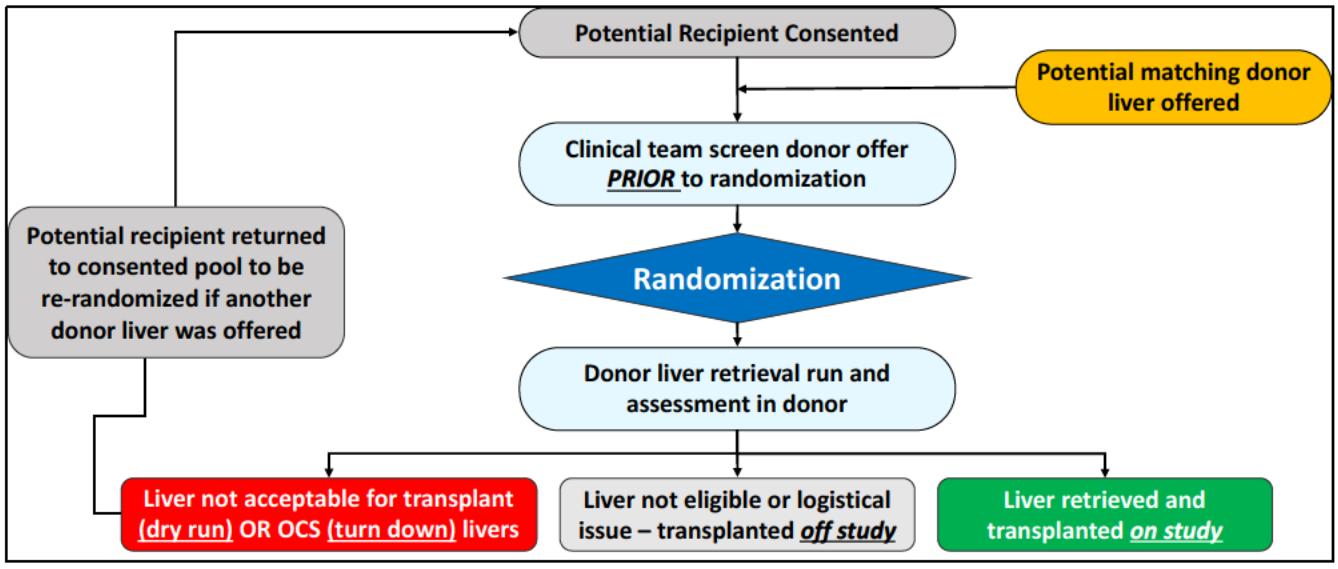
Given the complex, multi-step, multi-stakeholder process for donor liver assessment and procurement for transplantation, and the significant differences that exist between cold storage and OCS Liver perfusion preservation methods, the PROTECT protocol prespecified the following randomization process designed to *minimize any potential clinical bias of knowing the randomization assignment when the clinical decision was made to accept or decline a potential donor liver offer by the trial clinical team* (see Figure 6 below):

- Consented potential recipients remained on the waiting list without any randomization until a potential donor liver was offered to these consented patients;
- The transplant clinical team screened the donor offer prior to the randomization to perform an initial determination on the suitability of the donor organ for the patient

and eligibility of the donor for the trial based solely on the preliminary clinical information provided. This screening was done without any randomization assignment.

- If, based on the available clinical information, the donor liver appeared to meet clinical acceptance and also appeared to meet eligibility for the trial, the randomization process took place to assign the liver to preservation by either OCS or Control.
- The procurement team traveled to the donor site with the randomized preservation method for final physical examination of the donor liver for potential procurement.
- After physical examination of the liver in the donor abdomen, there were 3 possible scenarios:
  - Donor liver found to be acceptable for transplant and meets trial eligibility criteria – these donor livers were procured, preserved using the randomized method and transplanted into a recipient in the PROTECT trial;
  - Donor liver found to be acceptable for transplant, however, it did not meet the PROTECT eligibility criteria (e.g. presence of accessory vessels, etc.) or a logistical issue was encountered (e.g. donor family withdrew consent for research, etc.) - these livers were preserved using ischemic cold storage and were transplanted off-trial. The recipients of these donor livers were withdrawn from the PROTECT trial.
  - Donor liver found to be not acceptable for transplantation (dry run) or the donor liver was turned down based on OCS Liver assessment parameters (turned down). The potential recipients for these donor livers in this category were returned back to the consented pool to be re-randomized if and when another donor liver was offered for them. *This step was pre-specified in the PROTECT trial protocol to minimize any potential clinical bias of knowing the randomization assignment for a potential subsequent donor offer*.

Figure 6: OCS Liver PROTECT Trial Pre-specified Randomization Process



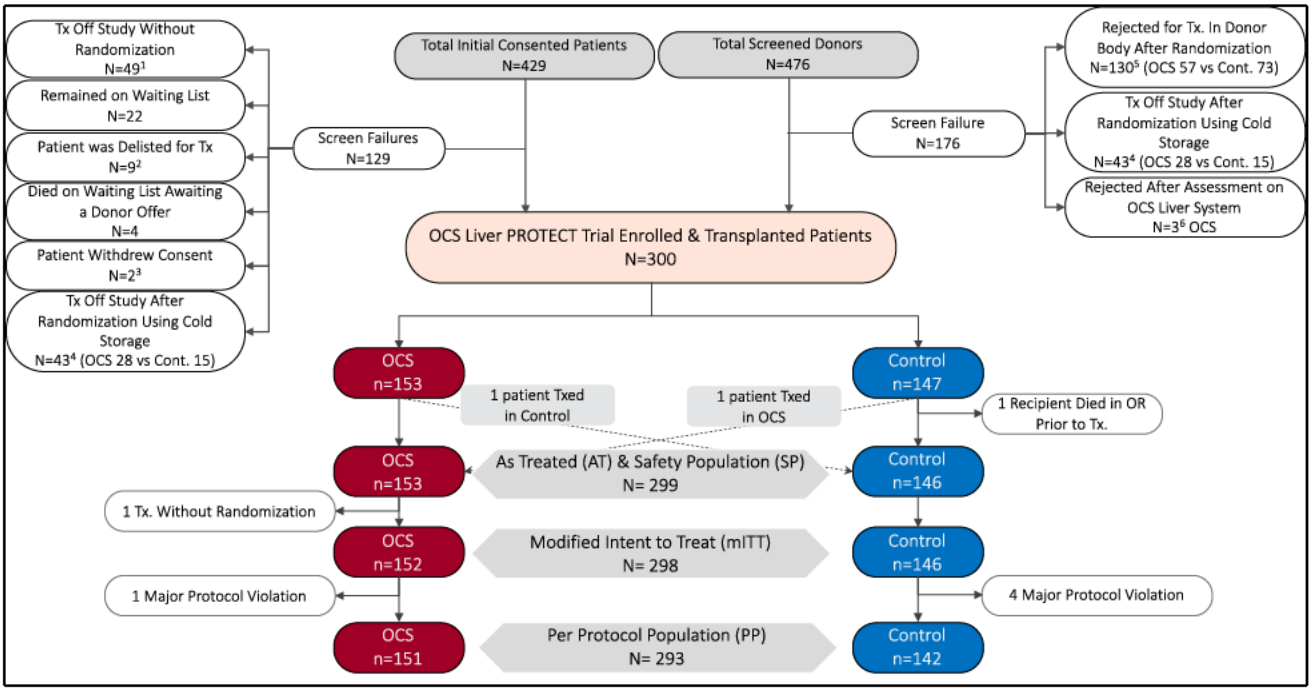
FDA asserts that the randomization process introduced bias in the clinical selection of donor livers in the PROTECT trial. TransMedics respectfully disagrees with this assertion based on the overall donor screen failures after randomization were balanced between the two treatment arms **OCS 85** (57 rejected for Tx. (dry runs) + 28 Tx. Off Study) vs. **Control 88** (73 rejected for Tx. (dry runs) + 15 Tx. Off Study).

1.6. PROTECT Trial Clinical Results

1.6.1. Trial Enrollment

Twenty (20) U.S. transplant centers were initiated, and 18 centers transplanted patients in the PROTECT trial. A total of 300 patients were enrolled and transplanted (OCS 153 and Control 147) between January 24, 2016 and October 15, 2019. The enrollment consort diagram is presented in Figure 7 below.

Figure 7: Enrollment Consort Diagram



[1] Transplanted (Tx) Off Study without Active Randomization Assignment After Initial Donor Offer(s) were Declined for Tx at Retrieval (N=49):

- N=25 – Subsequent donor liver offer did not meet OCS Liver PROTECT trial inclusion criteria.
- N=21 – Site PI decided not to re-randomize patients at donor offer due to donor operating room (OR) logistical reasons or lack of trial trained retrieval staff at time of donor offer.
- N=3 – Patients no longer met trial eligibility criteria due to deteriorating health status or received split liver transplant.

[2] Patient was Delisted for Tx (N=9: 6 OCS, 3 Control):

- N= 3 (2 OCS, 1 Control) – Metastatic cancer discovered at recipient surgical exploration.
- N= 4 (2 OCS, 2 Control) – Delisted for transplantation due to deteriorating health status.
- N= 2 (2 OCS, 0 Control) – Deemed ineligible for trial by site PI and was withdrawn.

[3] Patients Withdrew Consent for Trial (N=2: 1 OCS, 1 Control)

[4] Tx Off Study with Randomization Assignment Using Cold Storage (N=43: 28 OCS, 15 Control):

- N= 39 (24 OCS, 15 Control) – Donor liver did not meet eligibility due to presence of accessory vessels, liver hematoma, or required surgical vascular repair.
- N= 4 (4 OCS, 0 Control) – Logistical reasons, including:
  - Donor family not consenting to research (requirement of organ procurement organizations);
  - Unable to obtain pre-retrieval liver biopsy;
  - OPO delaying OR time resulting in trained trial retrieval team being off call; and
  - Recipient deterioration with renal insufficiency on day of transplant.

[5] Rejected for Tx in Donor Body After Randomization (N=130: 57 OCS, 73 Control):

- N=42 (18 OCS, 24 Control) – DCD donor did not expire within 30 mins.
- N=31 (9 OCS, 22 Control) – Clinical judgement at retrieval.
- N=27 (13 OCS, 14 Control) – Steatosis.
- N=9 (3 OCS, 6 Control) – Cirrhosis or fibrosis of the donor liver.
- N=4 (2 OCS, 2 Control) – Vasculature abnormalities or diseased.
- N=3 (3OCS, 0 Control) – Donor-recipient organ size mismatch.
- N=2 (2 OCS, 0 Control) – Liver or Kidney malignancy discovered during retrieval.
- N=12 (7 OCS, 5 Control) – Other reasons: re-allocation, donor did not progress or logistical reasons.

[6] DCD Donors Rejected for Tx After OCS Liver Assessment N=3

- N=2 – Rising lactate levels despite maximizing OCS Liver perfusion parameters.
- N=1 – Donor liver pre-retrieval biopsy revealed extensive bridging fibrosis.

FDA has raised a concern about the potential for randomization bias in favor of the OCS, but TransMedics does not believe that this concern is supported based on the following facts:

- The donor and recipient screen failures were justified by not meeting trial eligibility or for other logistical, or patient-related reasons.
- The overall donor screen failure after randomization was balanced between the treatment arms **OCS 85** (57 rejected for Tx.(dry run) + 28 Tx. Off study) vs. **Control 88** (73 rejected for Tx (dry run). + 15 Tx. Off Study).

1.6.2. Donor Demographic and Baseline Characteristics

The donor demographics and baseline characteristics are shown in Table 1. The donor organs used in this trial were associated with some clinical risk factors that may make them less likely to be used for transplantation due to the limitation of cold ischemic storage, e.g., donors with advanced age, multiple co-morbidities like steatosis, long cross-clamp time, or donation after circulatory death (DCD). In fact, ~60% of the donor livers in the study met more than one of these donor characteristics. Both donor groups were similar in risk factors of age ≥ 40 years, cross clamp time > 6 hours and macrosteatosis; however, the OCS arm included substantially more DCD donors. DCD liver transplantation is considered to be associated with higher clinical risks due to the impact of warm ischemic injury of the agonal phase on the incidence of EAD and ischemic biliary complications post-transplant (Mateo, et al., 2006; Mathur, et al., 2010, Lee et al., 2014).

Table 1: Donor Demographic and Baseline Characteristics (AT Population)

Parameter	OCS (N=152 [2])	Control (N=146)
Donor Age (years): mean ± SD	45.84 ± 14.90	46.96 ± 15.22
Cause of death		
• Cerebrovascular Hemorrhage	44 (28.9%)	50 (34.2%)
• Head trauma	35 (23.0%)	29 (19.9%)
• Cardiac	13 (8.6%)	10 (6.8%)
• Other (Anoxia, CSF infection, Suicide, Stroke)	60 (39.5%)	57 (39.0%)
Donor Characteristics [1]		
• ≥ 40 years old	102 (67.1%)	93 (63.7%)
• Total cross clamp ≥ 6 hours	48 (31.6%)	56 (38.4%)
• DCD ≤ 55 years old	28 (18.4%)	13 (8.9%)
• Steatotic liver > 0% and ≤ 40% macrosteatosis at time of retrieval	95 (62.5%)	86 (58.9%)

Parameter	OCS (N=152 [2])	Control (N=146)
• Multiple Donor Characteristics	95 (62.5%)	85 (58.2%)

(1) Multiple donor characteristics (inclusion criteria) could be met (total 60.4% of all donors).

(2) Does not include donor organ for Patient (b) (6) as this patient was not randomized.

1.6.3. Recipient Demographic and Baseline Characteristics

The recipient demographics and baseline characteristics are shown in Table 2. The majority of the recipients were males (66-69%), with a mean age of 57-58 years and a mean MELD score of 28. Almost a third of the recipients had a history of diabetes and the most prevalent primary diagnosis was alcoholic cirrhosis. The two treatment groups were similar in all demographic and baseline characteristics with no significant differences noted.

Table 2: Recipient Demographic and Baseline Characteristics (AT Population)

Parameter	OCS (N=153)	Control (N=146)
Recipient Age (yrs): mean ± SD	57.07 ± 10.33	58.59 ± 10.04
Gender		
• Male	102 (66.7%)	100 (68.5%)
• Female	51 (33.3%)	46 (31.5%)
BMI (kg/m^2): mean ± SD	29.67 ± 5.38	29.51 ± 5.51
MELD Score: mean ± SD Median	28.4 ± 6.90 29.0	28.0 ± 5.71 29.0
History of diabetes	44 (28.8%)	44 (30.1%)
History of liver cancer	60 (39.2%)	63 (43.2%)
Primary diagnosis		
• Cholestatic Diseases	9 (5.9%)	8 (5.5%)
• Chronic Hepatitis	27 (17.6%)	36 (24.7%)
• Alcoholic Cirrhosis	54 (35.3%)	48 (32.9%)
• Metabolic Diseases	6 (3.9%)	6 (4.1%)
• Primary Hepatic Tumors	14 (9.2%)	15 (10.3%)
• NASH	24 (15.7%)	20 (13.7%)
• Other	19 (12.4%)	13 (8.9%)

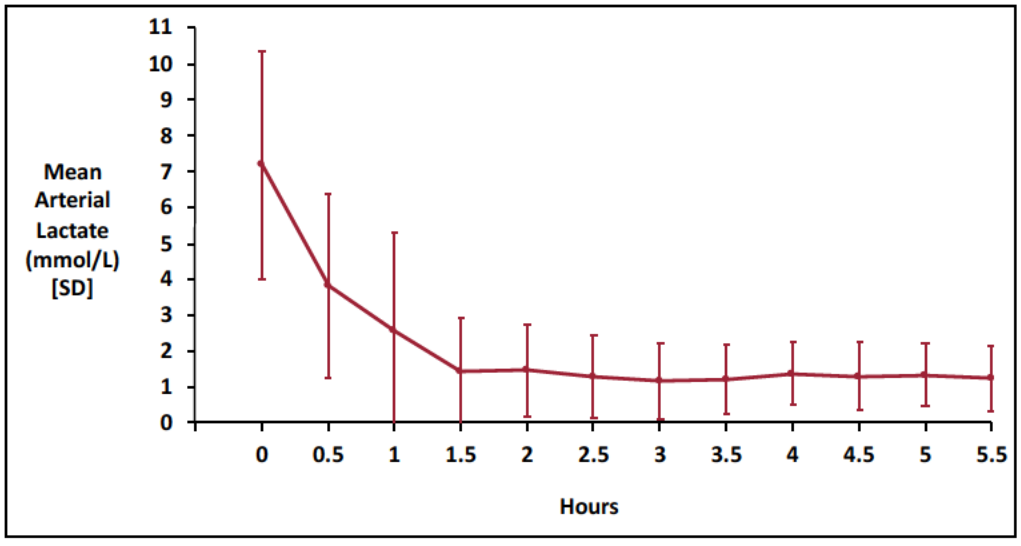
1.6.4. OCS Donor Liver Preservation and Assessment

Donor livers were perfused on OCS and were maintained in a near physiologic condition based on OCS perfusion parameters, bile production and blood gas results of the perfusate (Table 3 below). Importantly, the OCS Liver lactate trend showed steady declining and stable trend throughout perfusion indicating that the donor liver has recovered (i.e., been resuscitated) from the non-physiologic insult of organ donation and procurement to a metabolically active normal liver function. (Figure 8)

Table 3: OCS Liver Perfusion Parameters and Perfusate Chemistry Levels (AT Population)

OCS Perfusion Parameters and Perfusate Chemistry	OCS (N=152)
OCS Liver Perfusion Time (mins) - mean ± SD	276.6 ± 117.4
Hepatic Artery Pressure (mmHg) - mean ± SD	70.6 + 16.2
Hepatic Artery Flow (L/min) - mean ± SD	0.7 + 0.2
Portal Vein Pressure (mmHg) - mean ± SD	5.4 + 2.3
Portal Vein Flow (L/min) - mean ± SD	1.3 + 0.1
Total Bile Production (ml) - mean ± SD	28.3 + 15.9
pH - mean ± SD	7.43 + 0.1
PaO2 (mmHg) - mean ± SD	420.2 + 80.7
PCO2 (mmHg) - mean ± SD	41.5 + 14.6
HCO3 (mmHg) - mean ± SD	28.6 + 10.3

Figure 8: OCS Liver Perfusion Lactate Trend for Transplanted Livers in PROTECT Trial



The use of OCS Liver System altered the nature of the critical time from removal from the donor body to reimplantation into the recipient (i.e., total out of body or cross-clamp time). The use

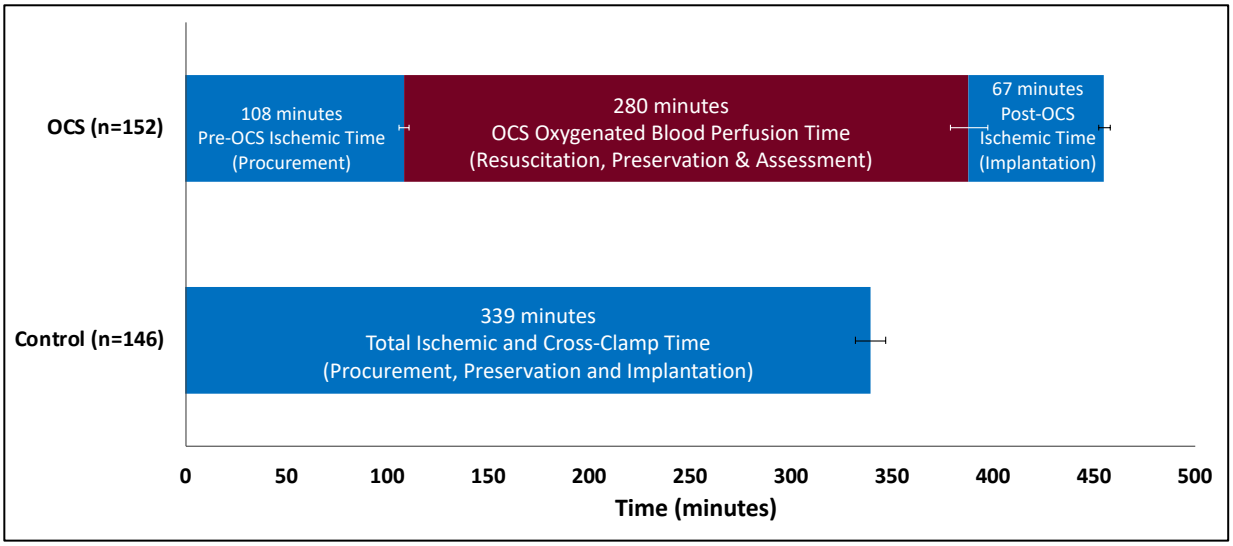
of the OCS Liver System significantly reduced the total cold ischemic time on the liver allografts by limiting the ischemic times to 2 obligatory time periods:

- **Pre-OCS Ischemic Time**: This is the time needed to surgically remove the donor liver from the body of the donor, perform the back table surgical preparation and instrument it on the OCS Liver System. The OCS instrumentation takes ~10-15 mins;
- **Post-OCS Ischemic Time**: this is the time needed to surgically reimplant the liver allograft into the recipient.

Otherwise, throughout the OCS perfusion, the conditions for the donor liver allograft were not ischemic given that it was perfused on OCS with warm, oxygenated blood perfusate until it was ready to be transplanted.

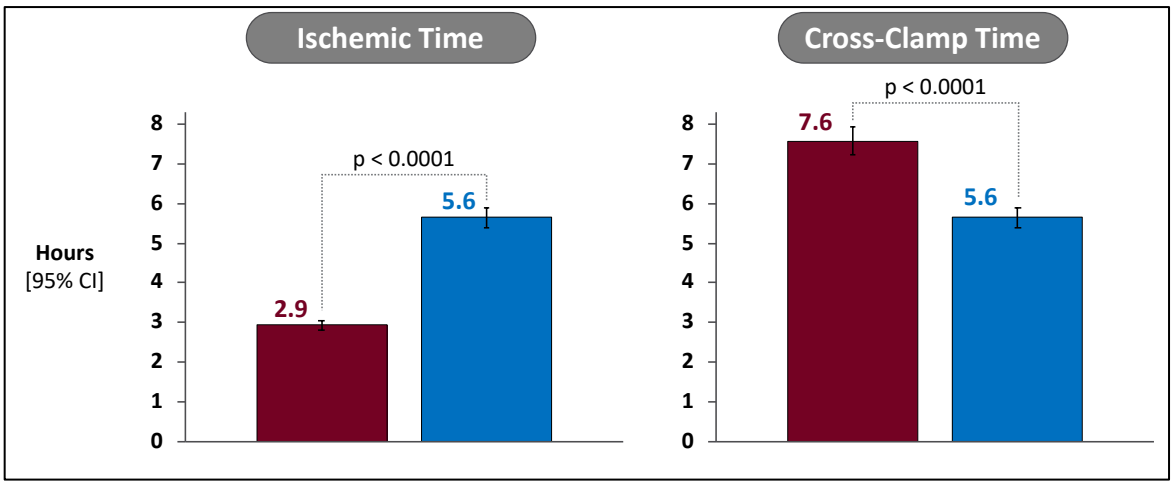
On the other hand, Control liver allografts were ischemic from the time they were procured from the donor body until they were implanted into the recipient. Figure 9 below demonstrates these critical time windows.

Figure 9: Overall Out of Body Times in PROTECT Trial



Based on the above unique characteristics of the OCS, the injurious total ischemic time was significantly reduced on the OCS Liver System compared to Control, despite the OCS having significantly longer total cross-clamp (out of body) time (Figure 10 below).

Figure 10: Total Ischemic and Cross-Clamp (Out of Body) Times in PROTECT Trial (mITT Population)



1.6.4.1. Donor Liver Clinical Turndown After Assessment on OCS Liver System

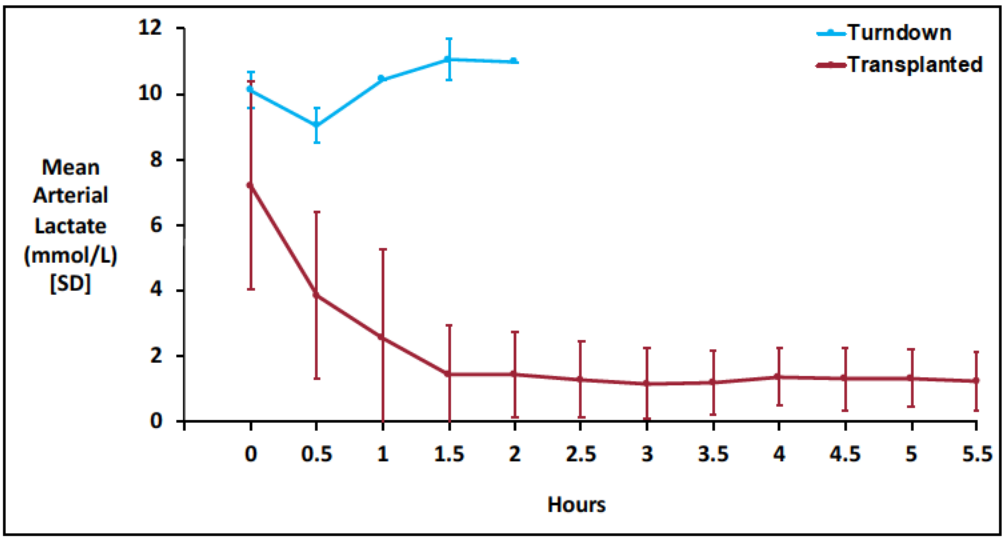
Given that the OCS Liver System enabled assessment of the donor livers ex-vivo, there were 3 DCD donor livers that were preserved and assessed on the OCS Liver System and were clinically turned down for transplantation due to rising lactate while being perfused on OCS Liver System in 2 cases and due to pre-retrieval pathology results in the third case. These 3 cases are described below:

- **Patient 1** (b) (6) **:** was randomized to OCS. The donor liver was perfused on the OCS for 1 hour and 42 minutes and was not accepted for transplantation due to the clinical decision by the accepting transplant surgeon due to pre-retrieval pathology results of widespread bridging fibrosis of the donor liver that was also confirmed by the accepting center's pathologist. The intended recipient remained in the study and was later transplanted with a liver preserved on OCS and is included in the PROTECT trial. The patient did not experience EAD and was alive at Day 366 with no graft failure.
- **Patient 2** (b) (6) **:** was randomized to OCS. The donor liver was perfused on the OCS for 2 hours and 46 minutes and was not utilized due to rising lactate levels while on OCS despite multiple attempts to maximize OCS Liver perfusion parameters. The starting lactate of 10.08 mmol/L and ending lactate of 10.98 mmol/L (See Figure 11 below). The core pathology lab examination revealed widespread hepatocyte cytoaggregation combined with early hepatocyte necrosis. The intended recipient remained in the study on the waiting list waiting for an organ match until PROTECT enrollment completion and was not transplanted in the study.
- **Patient 3** (b) (6) **:** was randomized to OCS. The donor liver was perfused on the OCS for 2 hours and 38 minutes and was not utilized due to rising lactate levels despite multiple attempts to maximize OCS Liver perfusion parameters. The starting lactate of 9.19 mmol/L and ending lactate of 10.25 mmol/L (See Figure 11 below). The core pathology lab examination revealed significant widespread hepatocyte cytoaggregation combined with early hepatocyte necrosis. The intended recipient remained in the study and was later re-randomized and transplanted in the

PROTECT trial in the Control arm. The patient experienced EAD and was alive at Day 353 with no graft failure.

In summary, the unique OCS Liver assessment capability provided a critical opportunity to the transplanting surgeon for additional clinical assessment, which resulted in a clearer understanding of the quality of the donor liver and led to an elimination of donor livers with significant pathology, maximizing safety for the transplanted recipients. These results represent a clinical benefit of the OCS Liver System compared to ischemic cold storage which does not enable any assessment of a donor liver allograft once it is removed from the donor body.

Figure 11: Mean OCS Liver Arterial Lactate Trend for Turned Down Donor Livers Compared to OCS Transplanted Donor Livers in PROTECT Trial



The FDA asserts that these 3 DCD donor livers that were turned down may have been injured on OCS resulting in their turn down. TransMedics respectfully disagrees with this assertion based on the following facts:

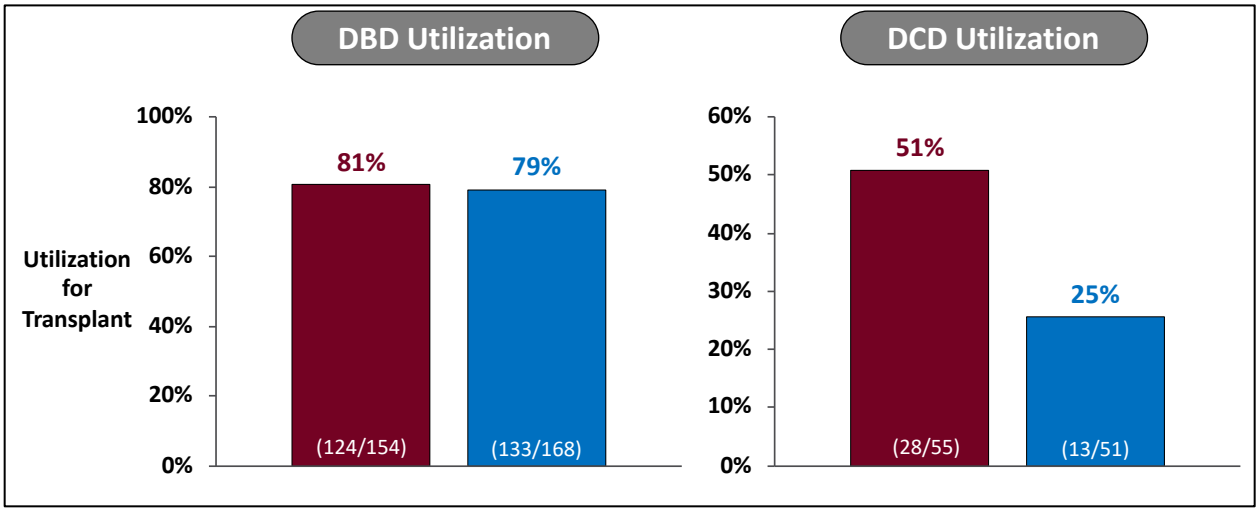
- 1 out the 3 donor livers was clinically rejected for transplantation based on pre-retrieval biopsy finding of bridging fibrosis that was validated by the accepting transplant center's pathologist. This clinical decision was independent of the OCS Liver use or perfusion.
- 2 out of the 3 DCD donor livers had a high initial circulating lactate that remained high or increased during perfusion despite multiple attempts to maximize OCS Liver perfusion to reverse this picture. This is clearly demonstrated in the results listed in Table 4 below.

Table 4: Comparison of OCS Liver Perfusion Parameters Between Transplanted Livers and 2 Turned Down Livers After OCS Assessment

OCS PROTECT Trial	Transplanted Liver Allografts (N=152)	Turned Down Liver Allografts (N=2)
Hepatic Artery Pressure (mmHg) – mean ± SD	70.6 ± 16.2	82 ± 8.9
Hepatic Artery Flow (L/min) – mean ± SD	0.7 ± 0.2	0.8 ± 0.07
Portal Vein Pressure (mmHg) – mean ± SD	5.4 ± 2.3	7.8 ± 0.5
Portal Vein Flow (L/min) – mean ± SD	1.3 ± 0.1	1.38 ± 0.07
Starting Lactate (mmol/L) – mean ± SD	7.2 ± 3.2	9.64 ± 0.63
Ending Lactate (mmol/L) – mean ± SD	1.2 ± 1.0	10.62 ± 0.52

Finally, we analyzed the impact of the preservation modality on donor liver utilization for transplantation from DBD and DCD donors in the PROTECT trial. Figure 12 below shows that the use of OCS resulted in significantly higher rates of utilizing DCD donor livers for transplantation compared to ischemic cold storage (Control). There was no difference in DBD donor liver utilization between the OCS and Control arms.

Figure 12: DBD and DCD Donor Liver Utilization Rates in PROTECT Trial

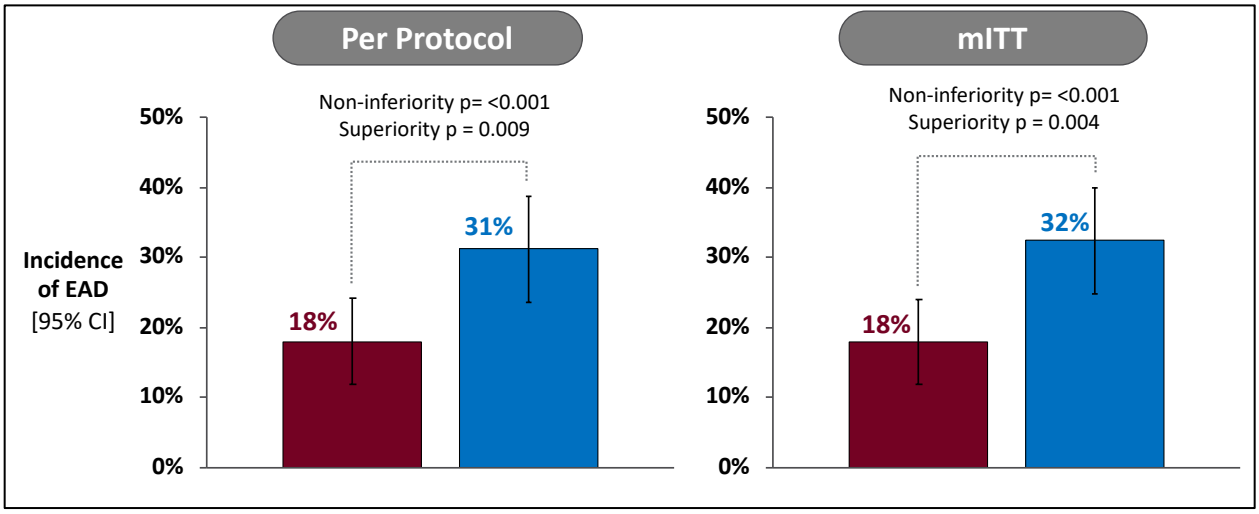


These data suggest that the OCS Liver System provided an additional opportunity for ex-vivo clinical optimization and assessment of the DCD liver grafts, resulting in doubling the yield of DCD livers transplanted (51% vs. 25%) compared to the Control arm. These results confirm the potential clinical benefits of machine perfusion to provide additional clinical assessments of the liver allografts. The ability to assess the donor livers allows transplant surgeons to gain more clinical confidence with the liver allograft and should increase the utilization of donor livers for transplantation and increase access for patients in need: in the U.S. DCD livers are seldom transplanted in the U.S. today due to concerns about ischemic/reperfusion injury of the graft and the potential for severe post-transplant ischemic biliary complications (Kwong, et al., 2020, Mateo, et al., 2006; Mathur, et al., 2010).

1.6.5. Primary Effectiveness Endpoint

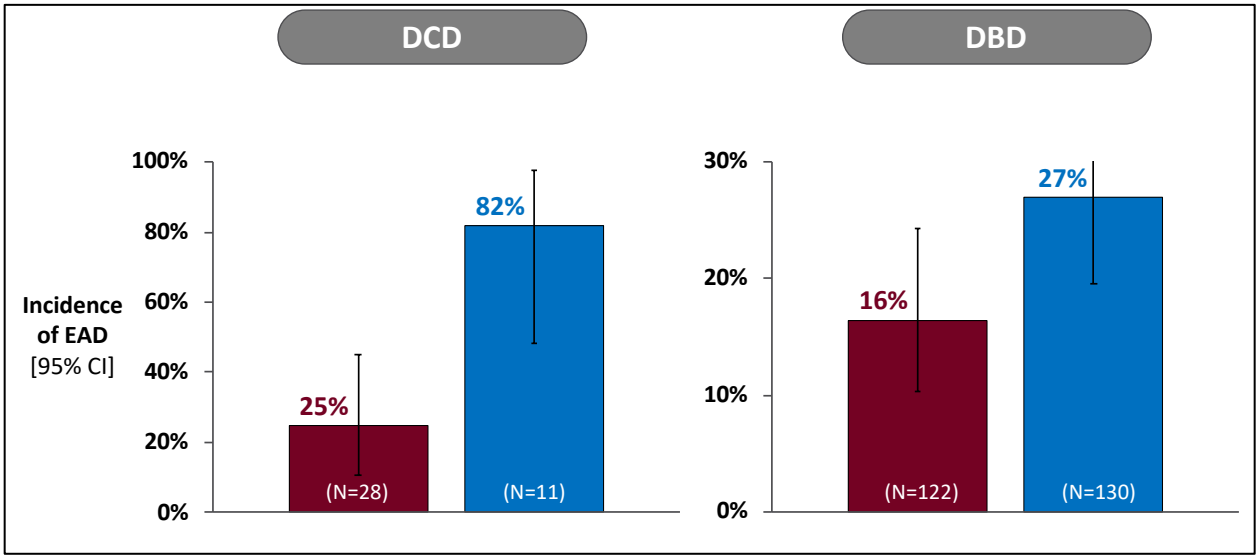
The OCS Liver PROTECT trial met its primary effectiveness endpoint by demonstrating statistical non-inferiority and superiority of outcomes of the OCS arm compared to Control in both the PP and mITT populations. Specifically, the results demonstrated that use of OCS Liver System was associated with a significant reduction of Early Allograft Dysfunction (EAD) compared to the Control in the primary analysis PP Population (OCS 18% vs. Control 31%, p=0.009). The same results were experienced in the mITT population (OCS 18% vs. 32%, p=0.004). See Figure 13 below.

Figure 13: Primary Effectiveness Endpoint - Incidence of Post-Transplant EAD (PP and mITT Populations)



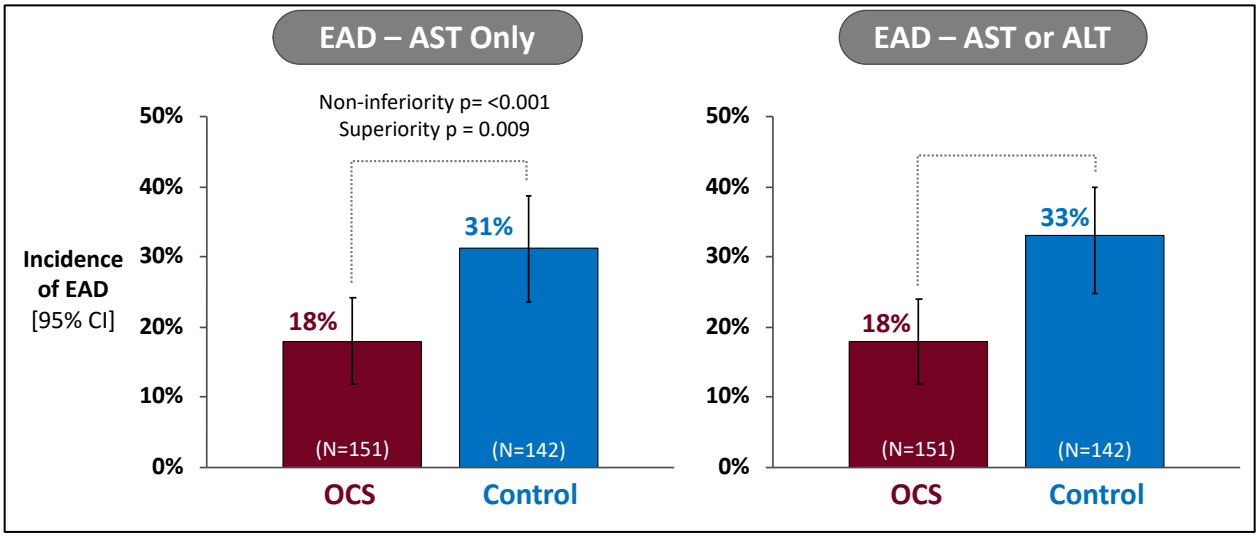
The same positive impact on EAD was experienced in both DBD and DCD donor cohort in the PROTECT trial. This finding further supports the robustness of the positive clinical impact of the OCS Liver System across both DBD and DCD donor livers.

Figure 14: Incidence of Post-Transplant EAD in DBD and DCD Donor Cohorts in PROTECT Trial (PP Population)



FDA has raised a concern about the definition of EAD used in the PROTECT trial, specifically, that it did not include ALT levels. To address FDA's issue, we collected ALT data for the PROTECT trial patients, performed a post-hoc sensitivity analysis of EAD based on both AST and ALT levels, and compared it to the pre-specified EAD primary effectiveness endpoint using only AST data. Figure 15 below demonstrates that the addition of ALT levels in the assessment of EAD did not change the overall conclusions and, in fact, resulted in an increased incidence of EAD in the Control arm. This further validates the robustness of using only AST to assess EAD and the robustness of the overall effectiveness endpoint of the PROTECT trial.

Figure 15: Post-hoc Sensitivity Analysis of EAD Based on AST and ALT Levels vs. the Pre-Specified EAD Assessment with AST only in PROTECT Trial (PP Population)



The FDA made several hypothesis-generating remarks about the validity of the different components of the broadly accepted EAD definition by Olthoff et al. (2010). TransMedics would like to respectfully clarify that these assertions are not relevant to the interpretation of the PROTECT Trial results and are not consistent with the published literature based on the following facts:

- The Olthoff et al. (2010) EAD definition is broadly accepted in clinical practice in liver transplantation in the U.S. It does not differentiate the contribution of the different components of the EAD definition;
- The EAD definition in PROTECT was pre-specified in the trial protocol and was approved by FDA without any issues or concerns raised by FDA throughout the trial enrollment;
- Elevated AST levels were the primary driver for EAD diagnosis in both OCS and Control trial arms, and elevated AST/ALT was shown by Olthoff to be associated with higher mortality and graft failure than other components:
- The same clinical picture was reported by another warm machine perfusion randomized trial in the UK (Nasralla et al., 2018)

Based on the above points, TransMedics asserts that the EAD results achieved in the EXPAND trial are clinically and scientifically valid.

1.6.6. Pathology Assessment

The PROTECT trial included an independent core pathology assessment of liver biopsies obtained pre- and post-transplant at 3 distinct sample time points (see Figure 16 below):

Sample 1: was taken to assess the condition of the donor liver prior to initiation of any preservation method. This is to provide a baseline picture of the donor livers studied in PROTECT.

Sample 2: was taken after the preservation period was completed and prior to transplantation into the recipient. This sample was taken only for hypothesis generation on the mechanism of potential pathological changes in the donor liver allograft.

Sample 3: was taken after transplantation and reperfusion of the donor liver allograft in the recipient's body. This sample represents the most clinically-relevant histological assessment point on the overall preservation and reperfusion injury histological markers in liver allografts. This is particularly true in the PROTECT trial because the preservation methods for OCS and Control differed substantially in that the Control liver was ischemic and not metabolically active, while the OCS liver was perfused, oxygenated, and metabolically active.

Figure 16: Pathology Sample Timepoints in PROTECT Trial

Histopathological evaluation of Sample 3 (post-transplant) demonstrated that the significant reduction of EAD associated with the use of OCS Liver System was validated mechanistically by the histopathological assessment. Independent and blinded histological assessment revealed substantially less moderate-severe lobular inflammation post-transplant for OCS livers. Lobular inflammation is a marker of ischemia and reperfusion injury (Ali, et al., 2015; Kakizoe, et al., 1990; Sosa, et al., 2016) (Figure 17 and Figure 18 below).

Figure 17: Post-Transplant Pathology Assessment – Overall Lobular Inflammation Severity in Biopsy Samples taken 90-120 minutes post-reperfusion in recipient abdomen (mITT Population)

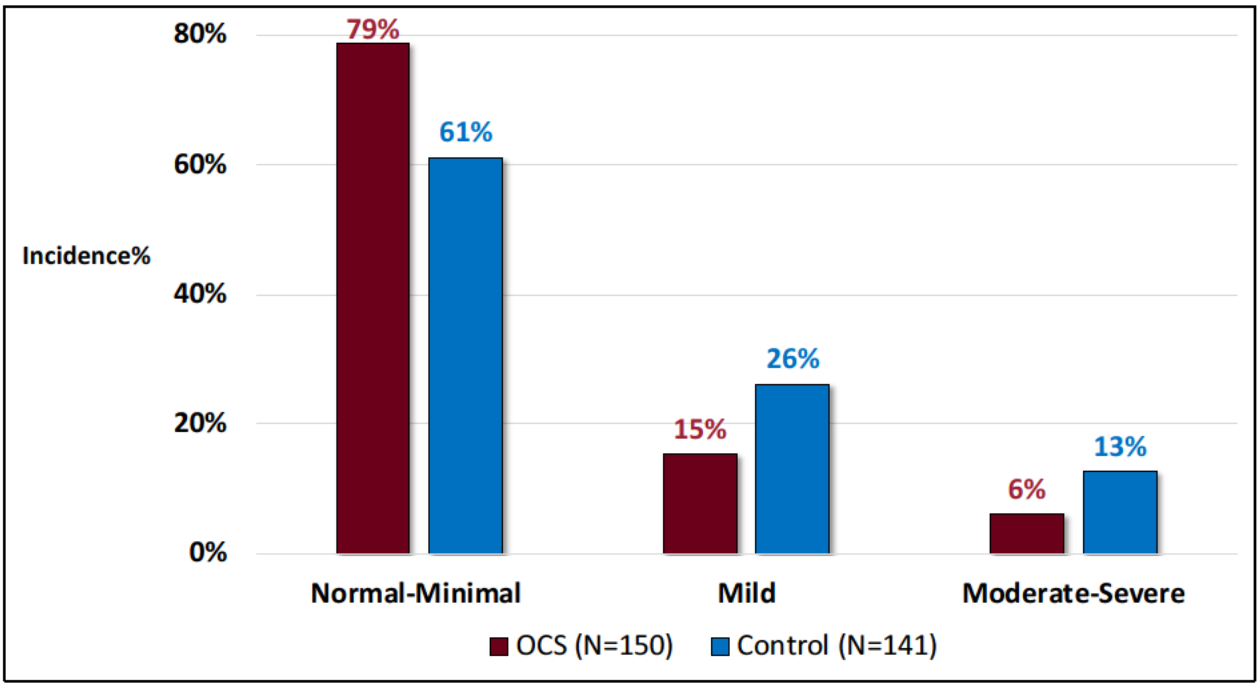
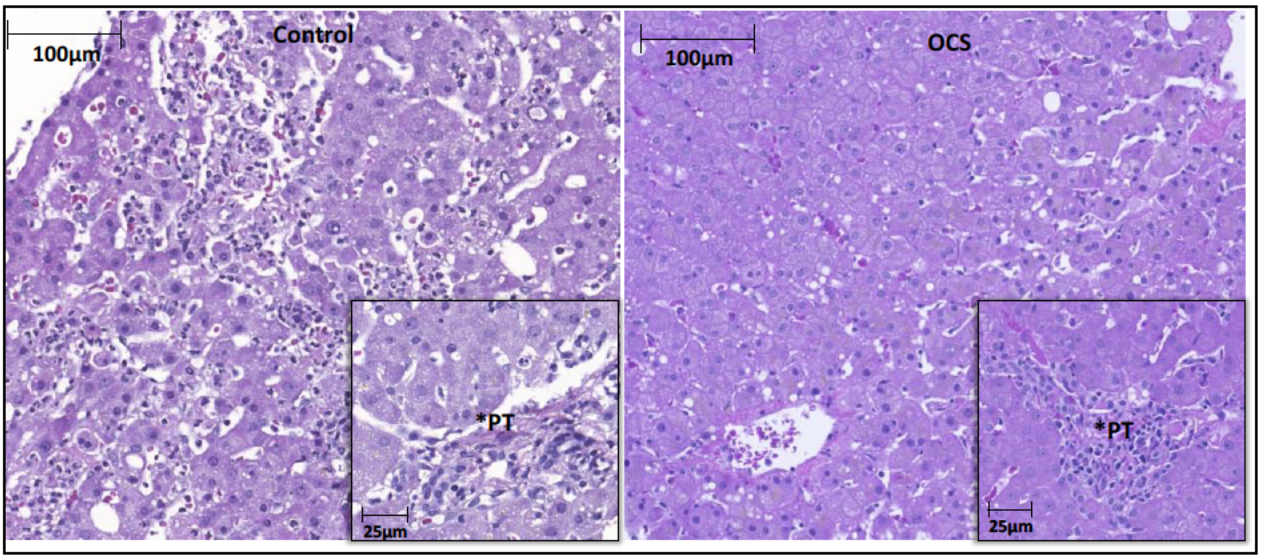


Figure 18: Post-Transplant Histology Representative Sample for Severe Lobular Inflammation from Biopsies Taken 90-120 minutes Post-reperfusion in Recipient Abdomen



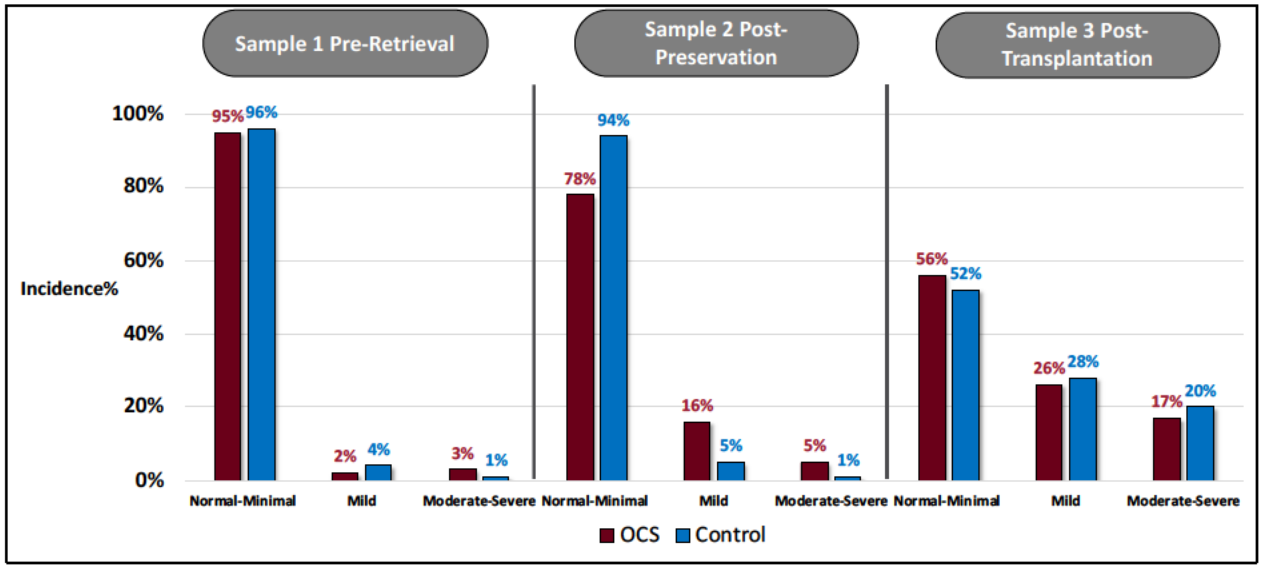
Representative histology to show an example of severe lobular inflammation in a Control (Left) liver post reperfusion with insert showing minimal portal inflammation, and OCS-treated liver (Right) showing absence of lobular inflammation and minimal portal inflammation, insert.

The FDA raised a concern in the panel briefing material about the slight increase in lobular necrosis in OCS vs. Control seen with the Sample 2 histopathological evaluation. The FDA asserted that these changes may imply that these donor livers may have been injured during

OCS perfusion. TransMedics respectfully refutes the FDA assertions given the lack of clinical evidence to support the FDA position and based on the following scientific and clinical facts:

- As outlined above, Sample 2 was taken immediately after preservation. It is important to note that the two preservation methods are significantly different and these differences impact Sample 2. In the Control arm, the liver allograft is in a non-metabolically active, cold ischemic state without any reperfusion. Therefore, from a clinical perspective, one should not expect to see any histological evidence of preservation injury in this control sample given the lack of perfusion. However, in the OCS arm, the liver allograft is perfused with oxygenated blood and is metabolically active. This OCS perfusion triggers the typical reperfusion process seen in all donor livers after the initial cold ischemia experienced during surgical procurement.
- Therefore, the most clinically relevant assessment is at Sample 3 given that at this point, samples from both arms have been subjected to the full spectrum of preservation and reperfusion in the recipient. Any changes seen in Sample 3 are most clinically reflective of the overall extent of any preservation injury experienced by the liver allograft.
- When we assessed the overall progression of lobular necrosis (from Sample 1 to Sample 3), there was no difference seen between the OCS and Control (see **Figure 19** below)

Figure 19: – Post-hoc Core Pathology Assessment of Overall Lobular Necrosis Changes in the PROTECT Trial

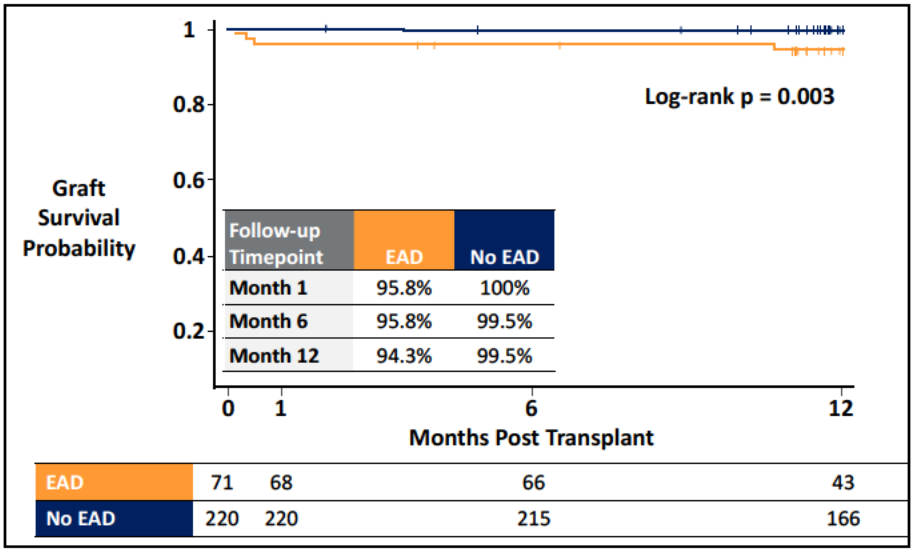


1.6.7. Clinical Benefits of Reducing EAD Post-Liver Transplantation

To address FDA's raised concern and to elucidate the major clinical benefits of reducing EAD post-liver transplantation, we performed post-hoc analyses stratifying key clinical outcomes of the PROTECT trial based on the presence or absence of EAD in the overall PROTECT trial population, similar to the approach taken by Olthoff, et al. (2010). The results showed that EAD was associated with:

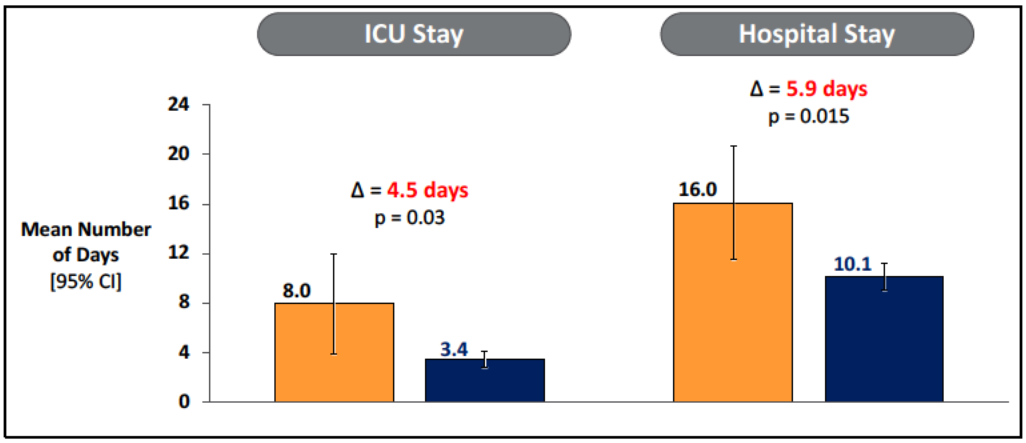
- Significantly increased risk for post-transplant graft failure. Graft failure is a serious and devastating clinical outcome for liver transplant recipients. Graft failure would require a re-transplantation, or the patient would die (see Figure 20 below).

Figure 20: Kaplan-Meier Liver Graft Survival for PROTECT Subjects (EAD vs. No EAD) (PP Population)



- Significant increase in Initial ICU and hospital length of stay post-transplantation. These findings show that the presence of EAD significantly increased hospital resource utilization and ultimately would increase the overall cost for the liver transplant procedure (see Figure 21 below).

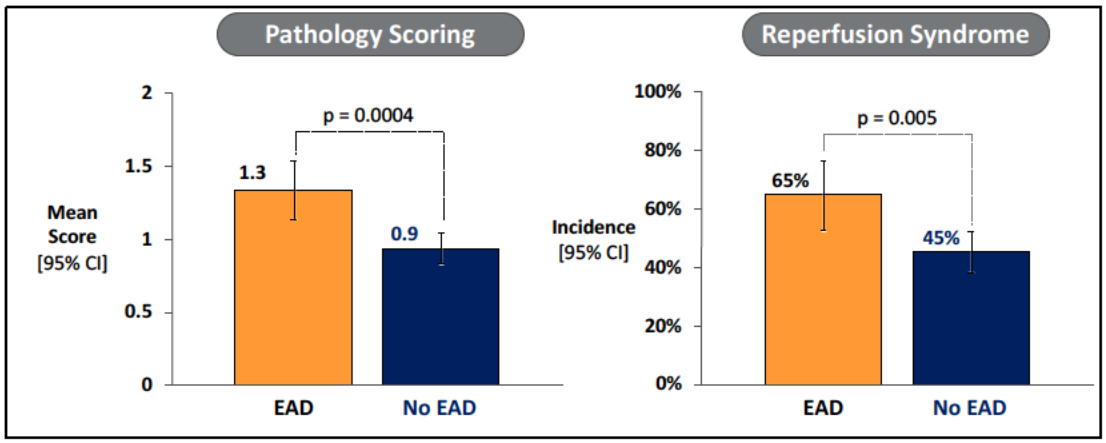
Figure 21: Length of ICU and Hospital Stay Post-Liver Transplantation (EAD vs. No EAD) (PP Population)



- Significant increase in the overall pathology score (which includes specific ischemia reperfusion injury pathological markers) for liver biopsies taken 90-120 minutes post-reperfusion in the recipient as assessed by independent blinded scoring by the core pathology lab (see Figure 22 below).
- Significant increase in post-transplant reperfusion syndrome where reperfusion syndrome is defined by an increase in lactate level over time, from anhepatic phase through ~120 minutes after reperfusion in the recipient abdomen. This result

indicates that recipients with EAD may be associated with a significantly higher risk of post-transplant hemodynamic instability, which could lead recipients to have a more complicated post-transplant clinical course (see Figure 22 below).

Figure 22: Post-Transplant Overall Pathology Scoring for Biopsies taken 90-120 Minutes Post-reperfusion (left) and Incidence of Reperfusion Syndrome (right) Based on Increase in Lactate Level from Anhepatic Phase Through Reperfusion in Recipient Abdomen (EAD vs. No EAD) (PP Population)



These results demonstrate that the ability of the OCS Liver System to reduce EAD would add significant clinical benefits for liver transplant recipients in the U.S. by potentially reducing the risk of graft failure, reducing time spent in the ICU and time spent in the hospital, as well decreasing the risk of hemodynamic instability post-transplant.

1.6.8. Secondary Effectiveness and OCS Donor Liver Assessment Endpoints

The OCS Liver PROTECT trial met all secondary effectiveness endpoints as described below.

1.6.8.1. OCS Liver System Assessment

An advantage of the OCS Liver System is that it allows for continuous monitoring of the donor liver during preservation. The measurements of lactate levels, bile production, hepatic artery pressure, and portal vein pressure were successfully obtained and measured during preservation.

Table 5: Secondary Endpoint – OCS Liver Assessment Parameters During Perfusion

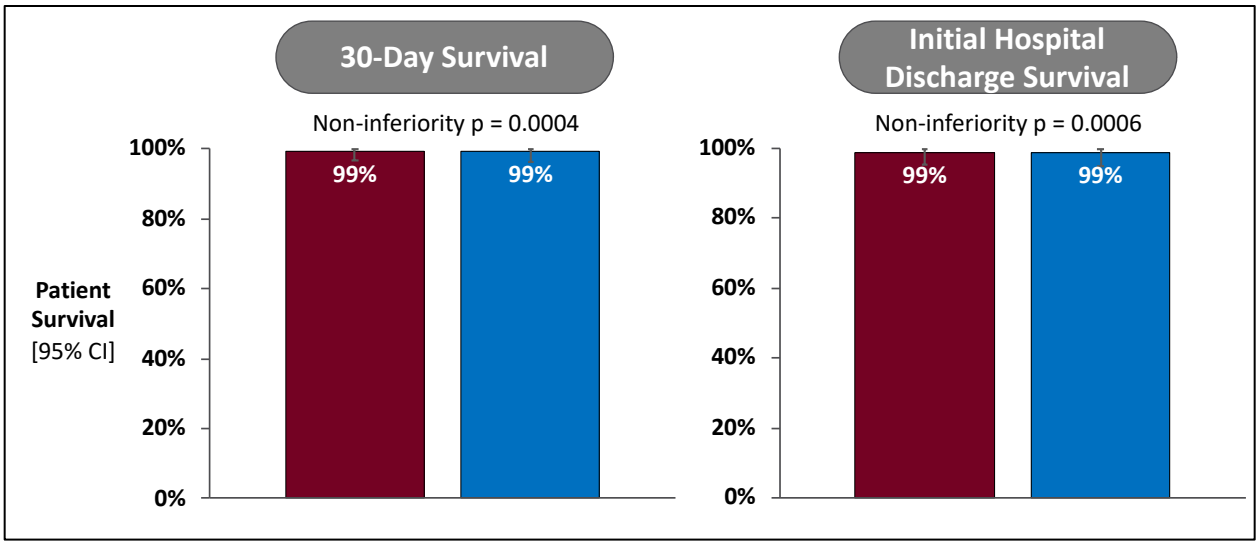
OCS Liver System Assessments During Perfusion	93% (144/155)	p-value 0.002*
Lactate Level	94% (145/155)	
Hepatic Artery Pressure	100% (155/155)	
Portal Vein Pressure	100% (155/155)	
Average Bile Production Rate	99% (154/155)	

* p-value from a one-sided exact binomial test, testing the null hypothesis that the true proportion is less than or equal to 0.85 vs. the alternative hypothesis that it is greater than 0.85.

1.6.8.2. Recipient Survival at Day 30 and at Initial Hospital Discharge

The OCS arm 30-day recipient survival and recipient survival to initial hospital discharge was high and statistically non-inferior to the Control arm in both the PP and mITT analysis. In the PP population, the 30-day survival for both the OCS and Control was 99% and the initial hospital discharge survival was 99% for both OCS and Control (see Figure 23).

Figure 23: Secondary Effectiveness Endpoint - Recipients' Survival at Day 30 and at Initial Hospital Discharge (PP Population)

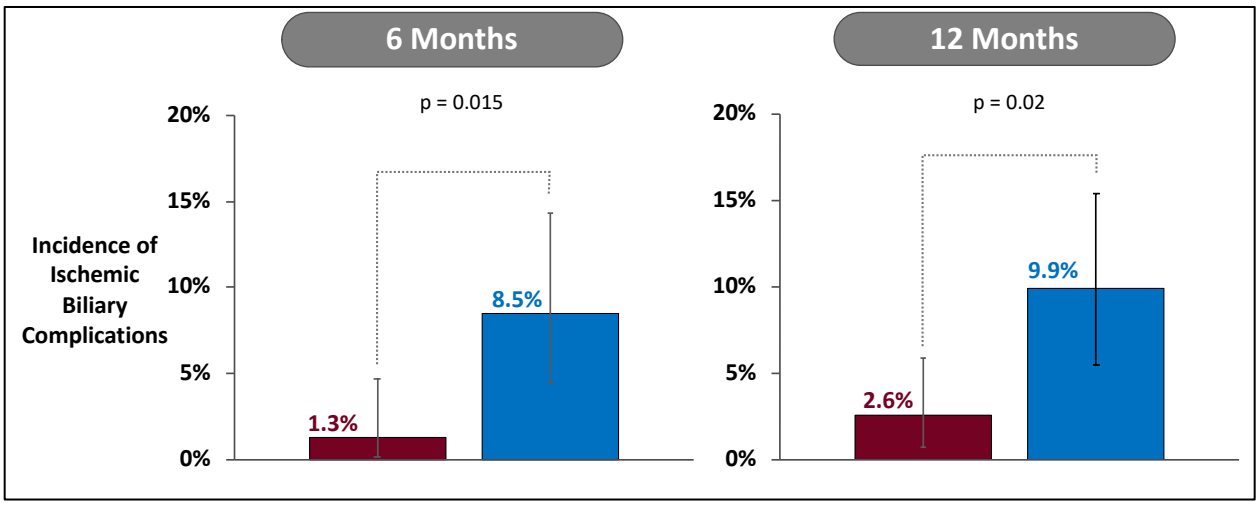


1.6.9. Other Clinical Endpoints

1.6.9.1. Incidence of Ischemic Biliary Complications at 6 and 12 Months

Ischemic biliary complications are one of the most serious complications that negatively impact long-term viability of the liver allograft and the patient. The OCS arm demonstrated a substantially lower incidence of ischemic biliary complications compared to the Control arm at 6 and 12 months follow-up in both the PP population (see Figure 24 below).

Figure 24: Incidence of Ischemic Biliary Complications Through 6 and 12 Months Post-Liver Transplant (PP Population)



1.6.9.2. Extent of Reperfusion Syndrome as Assessed by Recipient Lactate Levels Post-transplant

Reperfusion syndrome was more severe in the Control group compared to OCS, based on an analysis showing higher recipient mean lactate levels post-reperfusion in the Control group (see Table 6).

Table 6: Assessment of Reperfusion Syndrome – Recipients' Mean Lactate Levels Post-reperfusion in Recipient (mITT Population)

Timepoint	OCS Recipient Arterial Lactate (mmol/L) ± SD) N=152	Control Recipient Arterial Lactate (mmol/L) ± SD) N=146
Anhepatic	3.47 ± 1.706	3.55 ± 1.621
0-40 min after reperfusion	4.05 ± 2.092	4.57 ± 2.532
90-120/150 min after reperfusion	3.64 ± 2.220	4.33 ± 2.987

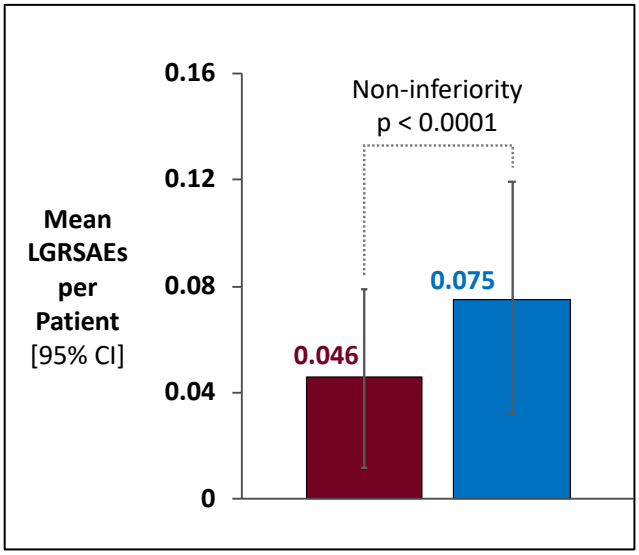
1.6.9.3. Post-transplant ICU Stay and Initial Hospital Stay

There was no difference in the length of initial post-transplant ICU and hospital stay for the OCS arm compared to the Control arm. The mean ICU stay was 107 hours for OCS compared to 111 hours for Control. The mean hospital stay was 12 days for OCS compared to 11 days for Control). However, as described above, there was a significant increase in initial ICU and hospital length of stay post-transplantation for subjects with EAD, and there was a higher incidence of EAD in the Control group compared to the OCS group.

1.6.10. Safety Endpoint

The OCS Liver PROTECT trial met its primary safety endpoint by demonstrating that the average number of LGRSAEs per patient within the first 30 days post-transplantation in the OCS arm was non-inferior to the Control arm (see Figure 25).

Figure 25: Safety Endpoint – Average number of LGRSAEs Per Transplanted Patient within the First 30 Days Post-Transplant (AT Population)



When analyzing the specific LGRSAEs as shown in Table 7 below, it is important to note that the OCS arm did not experience any ischemic biliary complications in the first 30 days post-transplant and was associated with a lower incidence of vascular complications compared to Control arm.

Table 7: LGRSAEs within 30 Days (AT Population)

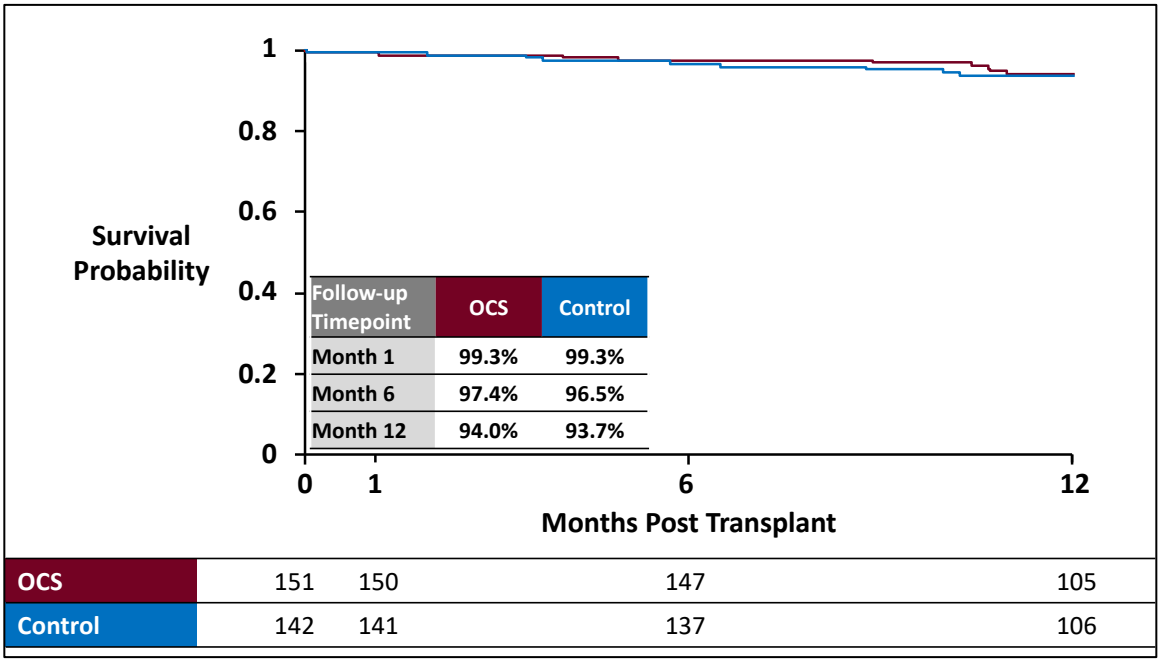
LGRSAE within 30 Days Post Transplant	OCS (N=153)		Control (N=146)	
	Patients	Events	Patients	Events
Any LGRSAE	7 (5%)	8	11 (8%)	13
Non-functioning graft	0	0	0	0
Ischemic biliary complication	0	0	2 (1%)	2
Vascular complication	7 (5%)	8	9 (6%)	11
Liver allograft infection	0	0	0	0

1.6.11. Overall Patient Survival

Overall patient survival was high and comparable between the OCS and Control arms. The 30-day patient survival for both arms is 99.3%. The patient survival is 97.4% and 96.5% at 6 months and 94.0% and 93.7% at 12 months for OCS and Control, respectively. See Figure 26 below.

All of the causes of death and liver graft relatedness have been CEC-reviewed and -adjudicated. The patient deaths are summarized in Appendix 3 of this document.

Figure 26: Kaplan-Meier Overall Patient Survival at Day 30 and through 6 and 12-Month Follow-up Visit (PP Population)

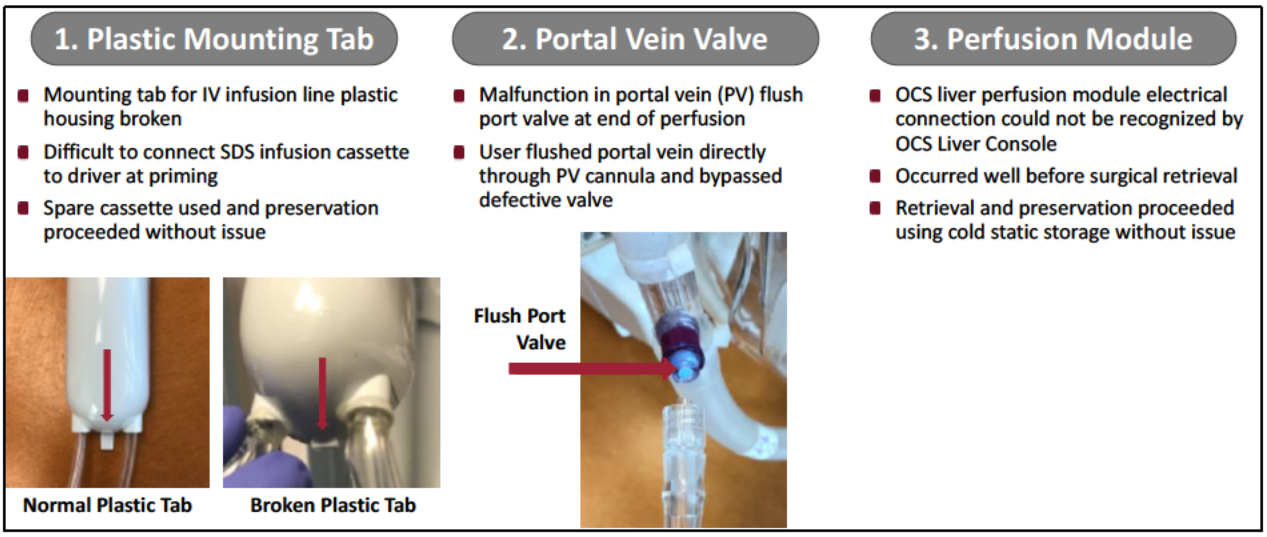


1.7. Reported Device Malfunctions in PROTECT Trial

In the OCS Liver PROTECT trial, there were 3 device malfunctions reported by trial centers (3/155 (1.9%)). Two of 3 malfunctions were of small plastic parts that are not a critical part of the perfusion of the donor liver, or the overall function of the OCS Liver System as further described below.

- One malfunction was reported in which a mounting tab for an IV infusion line plastic housing was broken, making it difficult to connect the Solution Delivery System (SDS) infusion cassette to the SDS driver at priming. This occurred prior to the donor liver instrumentation on the OCS Liver System (see Figure 27 below). In this case the user obtained a spare cassette and the preservation proceeded without any issues.
- One malfunction was reported for a portal vein (PV) flush port valve at the end of OCS perfusion and in preparation for cold flushing the donor liver in the recipient OR (see Figure 27 below). In this case, the user flushed the portal vein directly through the PV cannula and bypassed the defective valve.
- The 3rd malfunction occurred during pre-retrieval OCS preparation, when the OCS liver perfusion module electrical connection could not be recognized by the OCS Liver Console. This occurred well before the liver was even surgically retrieved. Thus, the retrieval and preservation proceeded using cold static storage without any issues.

Figure 27: Summary Device Malfunctions Reported in PROTECT Trial



Device malfunctions that were reported in the OCS Liver PROTECT trial did not subject the recipients to any harm given that 2 occurred well before retrieval. Importantly, all 3 donor livers were transplanted successfully to the recipients and their results were analyzed in the PROTECT trial.

1.8. DCD Liver Results

The overall PROTECT trial included both DBD and DCD donor livers. In the FDA panel briefing materials, the FDA referenced the British Transplant Society Guidelines on Transplantation from Deceased Donors after Circulatory Death (BTS, 2013), which lists a categorization for DCD donor quality. Although these guidelines were not used in the design of the PROTECT trial and were developed to guide liver transplantation outside the US., the FDA referenced these guidelines to assert that the PROTECT trial enrolled "ideal" DCD donor livers. To respond to this assertion, we prepared **Table 8** below to demonstrate that the large majority of PROTECT trial DCD donors were not ideal DCD donors, as asserted by FDA. Specifically, the OCS arm had 7.41% (2/27) ideal DCD donors vs. Control which 15.38% (2/13).

Table 8. The British Transplant Society DCD Guidelines Applied to PROTECT Trial DCD Donor Livers

Criteria	OCS DCD Livers (N=28) Number of Donors n/N (%)	Control DCD (N=13) Number of Donors n/N (%)
Donor age < 50	23/28 (82.14%)	12/13 (92.13%)
WIT <20 min	6/25 (24%)	4/12 (33.33%)
CIT <8 hours	20/28 (71.43%)	12/13 (92.31%)
Macrosteatosis <15%	27/28 (96.43%)	9/11 (81.82%)
Weight <100 Kg	21/28 (75%)	9/13 (69.23%)
Meet ALL Criteria (Ideal DCD Organ)	**2/27 (7.41%)**	**2/13 (15.38%)**

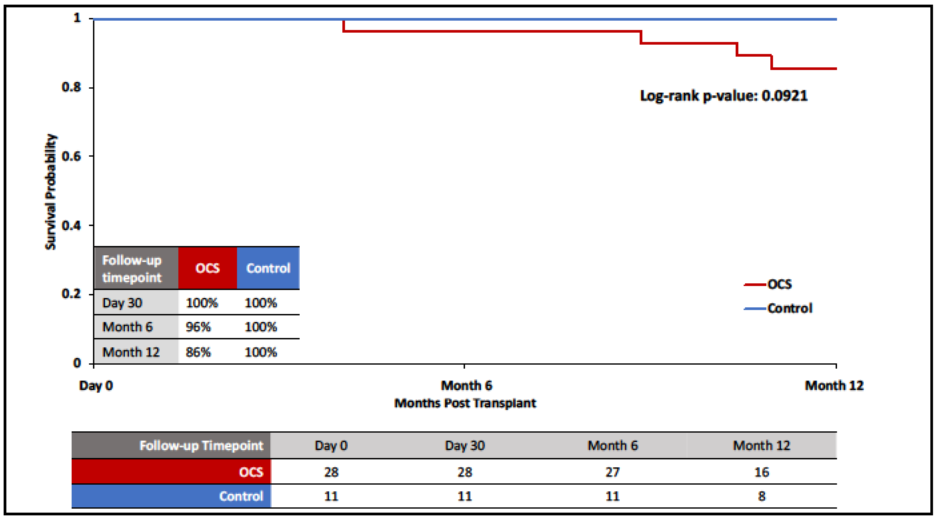
The overall patient survival in the DCD donor liver cohort was associated with comparable patient survival in both the OCS and Control arms of the PROTECT trial (see **Figure 28**). There

were 4 deaths through 12 months of follow up in the OCS arm for the DCD cohort. The causes of deaths for these 4 cases were:

- Patient 1 (b) (6) Patient expired 316 days post-transplant from metastatic recurrence of hepatocellular carcinoma
- Patient 2 (b) (6) : Patient expired 269 days post-transplant from recurrence of hepatocellular carcinoma
- Patient 3 (b) (6) : Patient expired 122 days post-transplant from sepsis
- Patient 4 (b) (6) Patient expired 333 days post-transplant at home from unknown causes.

Similarly, the DCD donor liver cohort was associated with good graft survival in both the OCS and Control arms of the PROTECT trial (see Figure 29 below), which shows 100% survival through 12 months. There was 1 graft loss in each arm after 12 months.

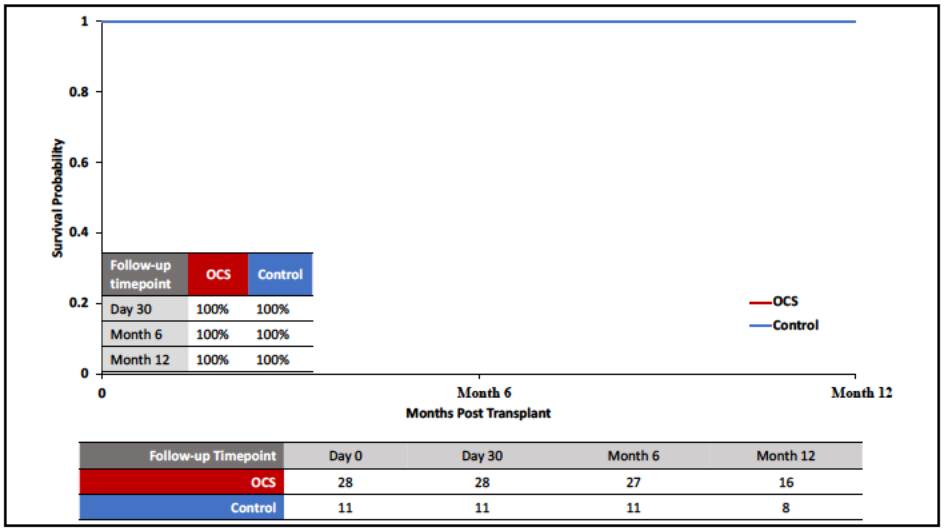
Figure 28: Kaplan Meir Analysis of Patient Survival in the DCD Liver Population (PP Population)



Follow-up timepoint	OCS	Control
Day 30	100%	100%
Month 6	96%	100%
Month 12	86%	100%

Follow-up Timepoint	Day 0	Day 30	Month 6	Month 12
OCS	28	28	27	16
Control	11	11	11	8

Figure 29: Kaplan Meir Analysis of Graft Survival in the DCD Liver Population (PP Population)



Follow-up timepoint	OCS	Control
Day 30	100%	100%
Month 6	100%	100%
Month 12	100%	100%

Follow-up Timepoint	Day 0	Day 30	Month 6	Month 12
OCS	28	28	27	16
Control	11	11	11	8

In conclusion, analysis of the results of the DCD liver cohort of the PROETCT trial demonstrated the following:

- The vast majority of the DCD donors used in the PROTECT trial did not meet the ideal DCD donor characteristics described in the British Transplant Society Guidelines;
- Graft survival achieved through 1 year post-transplant is favorable and is clinically acceptable;
- The OCS Liver assessment of donor liver allograft function provides additional clinical datapoints that may aid the clinical decision-making on the acceptability of these DCD donor livers for transplantation, thus potentially expanding the use of these DCD liver allografts currently seldomly used for transplantation.

1.9. Summary of the Clinical Results of the OCS Liver PROTECT CAP

The OCS Liver PROTECT Continued Access Protocol (CAP) was approved by FDA on November 14, 2019 under (b)(4) for 74 subjects. The PROTECT CAP is a single-arm study but otherwise the study design was the same as the OCS Liver PROTECT trial. The PROTECT CAP data are provided as a supplemental data set to the PROTECT trial which serves as the primary data set for this PMA.

A total of 74 subjects have been enrolled in OCS Liver PROTECT CAP. As of the database closure date of April 8, 2021, all 74 subjects have reached 30 days post-transplant, only 50 subjects have reached 6 months, and 19 subjects have reached 12 months. The study is on-going, and data are still being collected, monitored, verified, and adjudicated for all transplanted patients. A summary of the available data for these 74 subjects is provided in the sections that follow.

1.9.1. Donor Characteristics and Demographics

Donor demographics and characteristics are shown in Table 9 below. There have been no donor liver turndowns after OCS perfusion in the PROTECT CAP. The donor characteristics are similar, except that PROTECT CAP has a higher percentage of DCD donors (23% in CAP) compared to PROTECT (18%). DCD livers are generally considered as higher risk and are associated with higher rates of EAD and graft failure (Lee et al., 2014).

Table 9: Donor Demographic and Baseline Characteristics, OCS Liver PROTECT CAP

Parameter	OCS Patients (N=74)
Donor Age Mean ± SD	47.12 ± 13.804
Cause of Death	
• Anoxia (n (%))	37/74 (50.00%)
• Cerebrovascular/Stroke (n (%))	24/74 (32.43%)
• Head Trauma (n (%))	12/74 (16.22%)

Parameter	OCS Patients (N=74)
• CNS Tumor (n (%))	0/74 (0.00%)
• Other [1] (n (%))	1/74 (1.35%)
Donor Inclusion Criteria [2]	
• Donor age ≥ 40 years old (n (%))	50/74 (67.57%)
• Expected total cross clamp/cold ischemic time ≥ 6 hours (n (%))	33/74 (44.59%)
• Donor after circulatory death (DCD) with age ≤ 55 years old (n (%))	17/74 (22.97%)
• Steatotic liver greater than 0% macrosteatosis and less than or equal to 40% macrosteatosis at time of retrieval (n (%))	37/74 (50.00%)
• Multiple Donor Characteristics	43/74 (58.11%)
(1) Bacterial meningitis (2) Multiple donor characteristics (inclusion criteria) could be met.	

1.9.2. Recipient Demographic and Baseline Characteristics

Recipient demographic and baseline characteristics are shown in Table 10 below and are similar to the OCS Liver PROTECT trial, except that PROTECT CAP has a higher percentage of primary hepatic tumor (17.6% in CAP) compared to PROTECT (9.2%).

Table 10: Recipient Demographic and Baseline Characteristics, OCS Liver PROTECT CAP

Parameter	OCS Patients (N=74)
Age (years): Mean ± SD	57.01 ± 11.572
Gender:	
• Male	56/74 (75.68%)
• Female	18/74 (24.32%)
BMI (kg/m^2): Mean ± SD	29.18 ± 6.258
MELD Score: Mean ± SD	27.69 ± 6.034
Medical history	
• History of diabetes	22/74 (29.73%)
• History of liver cancer	30/74 (40.54%)
Primary Diagnosis	
• Alcoholic Cirrhosis	30/74 (40.54%)
• Cholestatic Diseases	5/74 (6.76%)

Parameter	OCS Patients (N=74)
• Chronic Hepatitis	12/74 (16.22%)
• Metabolic Diseases	1/74 (1.35%)
• NAFLD/NASH	10/74 (13.51%)
• Primary Hepatic Tumor	13/74 (17.57%)
• Other	3/74 (4.05%)
○ Cholangiocarcinoma	2/74 (2.70%)
○ Primary Biliary Cholangitis	1/74 (1.35%)

1.9.3. Primary Endpoint - Early Allograft Dysfunction (EAD)

EAD for all patients has been adjudicated by the CEC. Nineteen (19) patients experienced EAD within the first 7 days post-transplant, as shown in Table 11 below. The rate of EAD is slightly higher than that observed in the PROTECT trial. The difference in EAD between PROTECT and CAP is not statistically significant (p=0.2178, Fisher's Exact test).

Table 11: EAD Results, OCS Liver PROTECT CAP

	OCS Subjects (N=74)
EAD	19/74 (25.68%)
• AST level > 2000 IU/L within the first 7 postoperative days	15/74 (20.27%)
• Bilirubin ≥ 10 mg/dl on postoperative day 7	4/74 (5.41%)
• INR ≥ 1.6 on postoperative day 7	5/74 (6.76%)
• Primary non-functioning graft within the first 7 days	0/74 (0.00%)

1.9.4. Patient Survival/Graft Survival

By the date of database closure, all 74 patients met the 30-day post-transplant follow-up. The 30-day patient and graft survival were 98.7%. Long-term follow-up of the CAP patients is ongoing. To-date, a total of 5 deaths have occurred among the 74 patients. Summary of the causes of deaths reported were as follows:

- **Patient 1** (b) (6) 73 y.o. recipient with MELD score of 28, BMI of 40 and severely compromised cardiac function. Arrested several times intra-operatively and experienced DIC and pulmonary embolism requiring TPA administration during the transplant procedure. Liver function was negatively impacted due to severe hemodynamic compromise and DIC due to cardiac arrest. Patient expired on day 111 from generalized sepsis.
- **Patient 2** (b) (6) **:** 47 y.o. recipient with MELD score of 40 and diagnosis with alcoholic liver cirrhosis. The patient expired on day 30 due to sepsis secondary to perforated duodenal ulcer.

- **Patient 3** (b) (6) **):** 73 y.o. recipient with MELD score of 28. Patient expired on day 59 due to sepsis of respiratory origin.
- **Patient 4** (b) (6) **:** 57 y.o. recipient with MELD score of 15. Patient expired on day 75 due to respiratory failure secondary to pre-existing hepatopulmonary syndrome.
- **Patient 5** (b) (6) **):** 61 y.o. recipient with MELD score of 32. Patient expired on day 108 from respiratory sepsis secondary to mycobacterium lung abscess.

All of the causes of death and liver graft relatedness have been CEC-reviewed and -adjudicated. A summary of the deaths is provided in Appendix 4 of this document.

1.9.5. Summary of PROTECT CAP Results

A total of 74 subjects transplanted in the OCS Liver PROTECT CAP. The results for the OCS Liver PROTECT CAP to date are similar to those observed in the OCS arm of the OCS Liver PROTECT trial. Long-term follow-up is ongoing on all CAP patients.

1.10. Summary of Clinical Evidence Supporting the Approval of the OCS Liver System

The OCS Liver PROTECT trial is a large, multi-center, randomized, controlled trial in the U.S. that was conducted to evaluate the clinical impact of OCS Liver perfusion and assessment on post-transplant clinical outcomes in liver transplantation from DBD and DCD donors. The PROTECT trial results are the primary data set supporting this PMA for the proposed clinical indication.

The results of the OCS Liver PROTECT trial provide ample evidence of effectiveness, safety, and favorable benefit/risk profile to support the OCS Liver System approval for the proposed clinical indication:

OCS Liver System Demonstrated Effectiveness:

- The OCS Liver PROTECT trial met the primary endpoint and demonstrated statistical superiority in reduction of EAD in both PP and mITT populations compared to the Control arm. EAD is the most common severe complication after liver transplantation. EAD is associated with significant risk of graft failure, requiring re-transplantation and prolonged ICU and hospital stay, which negatively impact patients' clinical quality of life and healthcare resource utilization post-transplant.
- The OCS Liver PROTECT trial met all secondary effectiveness endpoints demonstrating that liver grafts can be assessed and monitored extracorporeally using the OCS Liver System.
- The use of the OCS Liver System demonstrated a clinically significant reduction of the most serious long-term post-transplant complication of ischemic biliary complications compared to Control at the 6 and 12-month follow-up timepoints in both the PP and mITT populations. Ischemic biliary complications negatively impact long-term viability of the liver allograft and patient survival.
- The use of the OCS Liver System resulted in significant reduction of ischemic time on the donor liver which resulted in less ischemia/reperfusion (IR) injury in the OCS arm compared to Control based on blinded pathological assessment.

- The OCS livers were associated with high and comparable patient survival at 30 days, at initial hospital discharge, and at 6 and 12 months compared to the Control arm.
- The results of the OCS Liver PROTECT CAP provide additional supporting evidence of the effectiveness of the OCS Liver System to preserve livers (including DCD livers) with a lower rate of EAD compared to Control arm of PROTECT.

OCS Liver System Demonstrated Safety:

- The OCS Liver PROTECT trial met its safety endpoint by demonstrating that the average rate of LGRSAEs in the OCS arm was statistically non-inferior to the Control arm.
- When analyzing the specific LGRSAEs, the OCS arm did not experience any ischemic biliary complications in the first 30 days post-transplant and was associated with lower incidence of vascular complications compared to Control arm.
- Rate of reported device malfunctions was low. Importantly, all 3 donor livers in these reported cases of device malfunction were transplanted and analyzed successfully in the results of the OCS Liver PROTECT trial. There was no increased risks or additional risks observed to donor organs or recipients as a result of these reported incidents.
- There were no safety signals seen in patient mortality, graft survival, or LGRSAEs. Serious Adverse Events (SAEs) were those typically experienced post-liver transplant and were similar for the OCS and Control groups.

The OCS Liver System Demonstrated Favorable Public Health Benefit/Risk Profile by:

- Positively impacting DBD and DCD donor liver utilization for transplantation
- Significantly improving post-transplant clinical outcomes

Clinical benefits associated with OCS Liver positive impact on DBD and DCD donor organ utilization for transplantation:

- The OCS Liver System significantly reduced ischemic injury/time on donor livers despite long out of body time. This capability may potentially enable safe distant liver procurement to maximize utilization of the donor liver allografts from both DBD and DCD donors;
- OCS Liver System's assessment capabilities resulted in two distinct potential clinical benefits in liver transplantation:
  - Substantial increase in DCD donor liver utilization for transplantation (i.e., OCS 28/55 (51%) vs. Control 13/51 (26%)); and
  - It enabled more clinical datapoints to be evaluated *ex-vivo* that may have assisted in the identification of hidden pathologically damaged DCD liver allografts, protecting the intended recipients from potentially poor outcomes.

Broader utilization of DBD and DCD livers for transplantation in the U.S. would be a substantial clinical public health benefit to meet the growing demand for liver transplant therapy, and could potentially reduce the waiting list mortality for patient waiting for a liver transplantation.

Clinical benefits associated with OCS Liver improved post-transplant clinical outcomes:

- The use of the OCS Liver System was associated with a significant reduction in incidence of EAD post-liver transplantation. The data in the PROTECT trial as well as studies in the literature demonstrate that the reduction of EAD is associated with:
  - Significant reduction in risks for post-transplant graft failure;
  - Significant reduction of post-transplant ICU and hospital length of stay of transplant recipients;
  - Significant reduction of liver allograft ischemia/reperfusion injury based on histological assessment; and
  - Significant reduction in post-transplant reperfusion syndrome for transplant recipients as assessed by recipients' lactate levels post-transplantation.
- The use of the OCS Liver System was also associated with a clinically significant reduction of ischemic biliary complications at 6 and 12 months post-transplant.
- There were no safety signals with a low number of LGRSAEs.

Improved clinical outcomes after liver transplantation would be a significant public health benefit as it would make liver transplant outcomes more successful while potentially reducing post-transplant healthcare resource utilization.

In conclusion, the OCS Liver PROTECT trial was the first-of-its-kind trial to target a specific group of DBD and DCD liver donors that may be challenging to utilize with cold storage. Achieving the above superior clinical effectiveness and safety outcomes should enable expansion of donor liver utilization from DBD liver allografts and expansion of the donor pool by using DCD liver allografts to help end-stage liver failure patients access this curative transplant therapy.

2. BACKGROUND – CLINICAL NEED FOR OCS TECHNOLOGY

Today, liver transplantation is universally accepted as the only curative treatment option for end-stage liver disease secondary to acute fulminant hepatic failure, several forms of liver cancers, and metabolic disorders. Today, there are several clinical challenges facing liver transplant therapy:

- ***Shortage of donor liver allografts*** - The availability of donor liver allografts has not kept pace with the demand[2]. The utilization of available DBD donor livers and the utilization of DCD donor livers are severely restricted by the limitations of cold ischemic storage of donor livers.
- ***High waiting list mortality of end-stage liver patients awaiting liver transplantation*** due to the shortage of supply of suitable donor livers for transplantation. The 2019 SRTR/OPTN Annual Report shows 35% mortality of the liver transplant waiting list in the US.

[2] This background and summary are focused on organs from deceased donors, which make up the majority of liver transplants today, and are appropriate for use of the OCS Liver System. The number of living donor transplants is relatively small: UNOS reported 8,415 deceased donor liver transplants for 2020, and 491 living donor liver transplants during this same year.

- ***High post-transplant complications in the form of Early Allograft Dysfunction (EAD) and Ischemic Biliary Complications (IBC)*** – Both are associated with short- and long-term graft failure and increased morbidity (Olthoff, et al., 2010; Hudcova, et al., 2017).
- ***Lastly, the donor pool is increasingly made up of higher risk donors (older age, complex medical history, etc.)*** – which impacts recipient outcomes and further complicates the clinical acceptance of these challenging donors for transplantation (MacConmara, et al., 2020).

The primary driver of the above clinical challenges are the significant limitations of ischemic cold storage which has been used for 40+ years to preserve donor livers. These limitations hamper the clinicians' ability to maximize donor liver utilization for transplants and are correlated with negative post-transplant clinical outcomes. These limitations include:

- Severe time-dependent ischemic injury to the donor liver, which correlates with the development of post-transplant complications like early allograft dysfunction (EAD) and ischemic biliary complications, which are associated with a significant risk of graft loss and increased risk of morbidity and mortality. Importantly, this limits the geographical time/distance for procuring donor livers for transplantation.
- No capability to optimize/resuscitate the liver allograft from the non-physiologic sub-optimal environment of organ donation from brain dead donors (DBD) or donors after circulatory death (DCD).
- No ability to assess liver allograft viability for transplantation after it has been removed from the donor body.

The OCS Liver System was designed to overcome the above limitations of ischemic cold storage. The OCS maintains the donor liver in a non-ischemic, metabolically active and functioning state (producing bile) by perfusing the liver with a warm, oxygenated, and nutrient-enriched blood-based perfusion solution. The OCS enables metabolic recovery and optimization of the donor liver from the challenging environment of brain death and DCD donation, by maximizing substrate delivery, replenishing key hormones and administration of vasodilators and broad-spectrum antibiotics, etc. The OCS Liver System is intended to reduce ischemia and reperfusion injuries on the donor livers and enable metabolic and functional assessment of donor livers to assess their suitability for transplantation.

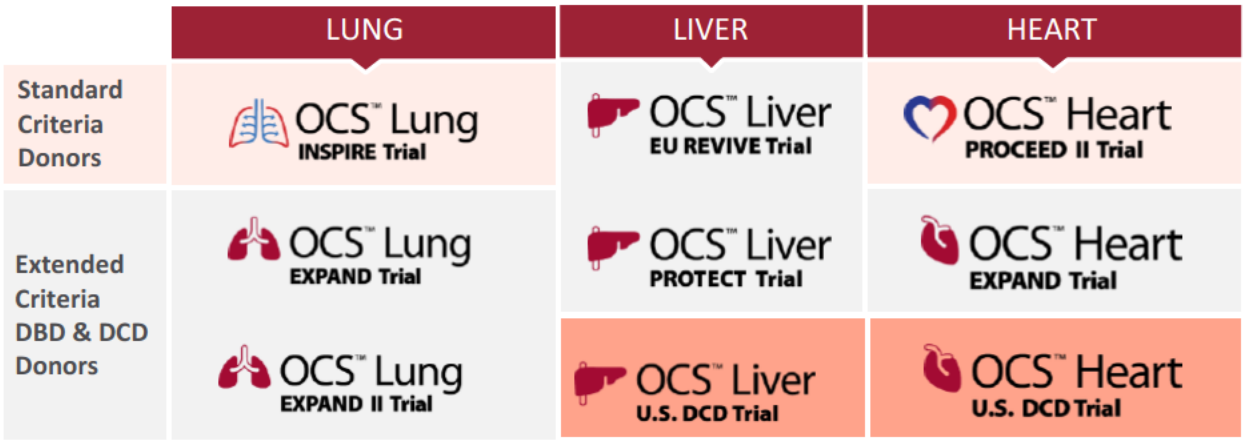
3. COMPANY AND DEVICE BACKGROUND

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 30) for use of the device platform 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 the limitations of cold storage.

- OCS Heart System PMA for DBD hearts is under review by the FDA and a pivotal IDE for DCD hearts has completed enrollment and will be submitted for FDA review.
- OCS Liver System PMA for DBD and DCD donor livers which is under review and is the focus of this Panel meeting.

Figure 30: 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 12 below.

Table 12: 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 (Lung INSPIRE)	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 (Lung EXPAND and EXPAND II)	FDA Approved on May 31, 2019
(b)(4)	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 (Heart EXPAND)	Under review by FDA

FDA Submission	Device	Organ	Overview	Current Status
(b)(4)	OCS Heart	DCD donor hearts	Pivotal trial to demonstrate safety and effectiveness of OCS Heart to resuscitate, preserve and assess DCD hearts for transplantation (Heart DCD)	Enrollment completed and trial is in follow-up phase, received FDA Breakthrough Device status for this trial
(b)(4)	OCS Heart	DCD donor hearts	Continued Access Protocol (CAP) for the OCS Heart DCD trial	Currently enrolling, received FDA Breakthrough Device status for this trial
(b)(4)	OCS Liver	DBD livers with age ≥ 40 years and/or expected cross-clamp time ≥ 6 hrs and/or steatotic livers with < 40% macrosteatosis and DCD livers ≤ 55 years old	Randomized, controlled pivotal trial of the OCS Liver System compared to standard of care cold storage preservation (Liver PROTECT)	PMA under review by FDA and is the focus of this Advisory Panel meeting
(b)(4)	OCS Liver	DBD livers with age ≥ 40 years and/or expected cross-clamp time ≥ 6 hrs and/or steatotic livers with < 40% macrosteatosis and DCD livers ≤ 55 years old	Continued Access Protocol (CAP) for the Liver PROTECT trial	Results for 74 patients included in the PMA under review
(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 (Liver DCD)	Currently enrolling, received FDA Breakthrough Device status for this trial

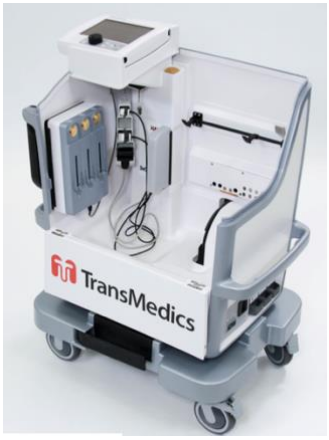
4. DEVICE DESCRIPTION – OCS LIVER SYSTEM

The OCS Liver System consists of:

- the OCS Liver Console (Liver Console)
- the OCS Liver Perfusion Set (LvPS) – comprised of Liver Perfusion Module (LvPM) and LvPS Accessories
- the OCS Bile Salts Set – composed of Sodium Taurocholate, which is infused to the circulating perfusate to replenish bile salt levels during *ex-vivo* perfusion on the OCS Liver System.

The current version of the OCS Liver System consists of Liver Console 1.0, Software 3.2.5-C, and LvPS 1.0.

4.1. Liver Console



The Liver Console is the reusable, non-sterile portable base unit for the OCS Liver System that includes the Wireless Monitor, fluid pumping subsystems (SDS and Circulatory (Pulsatile) Pump), probes, gas cylinder, power subsystem (including batteries), SD Data Card, Mobile Base, and electronics and software. The Wireless Monitor displays perfusion parameters and system status and allows the user to adjust specific system settings during transport of the donor liver. The Liver Console provides a rigid compartment to house and protect the Liver Perfusion Module (LvPM) during transport.

4.2. Liver Perfusion Set (LvPS)

The LvPS consists of the Liver Perfusion Module (LvPM) and the disposable LvPS Accessories.

The LvPM is a sterile, single-use device that holds, protects, maintains, and supports the liver during preservation and transport. The LvPM encompasses the perfusate and organ-contacting components and interfaces with the Liver Console. The LvPM contains the organ chamber and the perfusion circuit, provides a physical conduit to circulate and oxygenate perfusate, incorporates various sensors, warms and pumps the perfusate, and provides mechanical and electrical interconnects with the Liver Console. The Wireless Monitor allows the user to observe measurements made within the LvPM.

The LvPS also includes the sterile, disposable accessories necessary to instrument the liver and manage the addition and removal of perfusate. The LvPS Accessories are as follows:

- OCS Liver Perfusion Initiation Set
- OCS Liver Instrumentation Tool Set
- OCS Liver Solution Infusion Set
- OCS Liver Perfusion Termination Set.

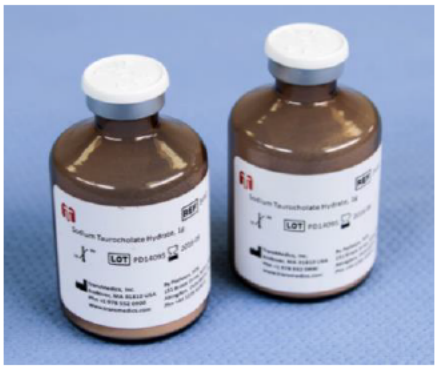
The LvPS Accessories are intended to: prime the LvPM; infuse solutions; connect the liver to the LvPM perfusion circuit; and, before removing the liver, provide cold flush to the liver.

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

- Clamshell-type, liver-specific polycarbonate chamber

- Perfusate sampling ports
- Integrated circulatory (pulsatile) pump head interface
- Integrated low-shear titanium perfusate warmer
- Integrated perfusate oxygenator (i.e., gas exchanger)
- Integrated sensors (pressure and temperature) and circuitry to communicate with the Liver Console.

4.3. OCS Liver Bile Salts Set



The OCS Liver Bile Salts Set consists of two glass vials of gamma-sterilized bile salts. Each vial contains one gram of Sodium Taurocholate per vial.

At the time of use, the OCS Liver Bile Salts are reconstituted with Sterile Water for Injection and then delivered to the perfusate in the LvPM circuit through the Liver Solution Infusion Set and controlled by the SDS. The bile salts introduced to the LvPM are intended to replenish the bile salts consumed by the liver during preservation. The OCS Liver Bile Salts are not intended to be administered to the donor or the recipient. Prior to transplantation into the recipient, the donor liver is flushed on the OCS.

4.4. Mode of Action

The OCS Liver System preserves the liver in a near-physiological, functioning state by perfusing the liver with a continuously-circulating mixture of (b)(4) perfusate supplemented with nutrients and oxygen in a controlled and protected environment referred to as the circuit. The perfusate consists of (b)(4) as described in in Table 13 below.

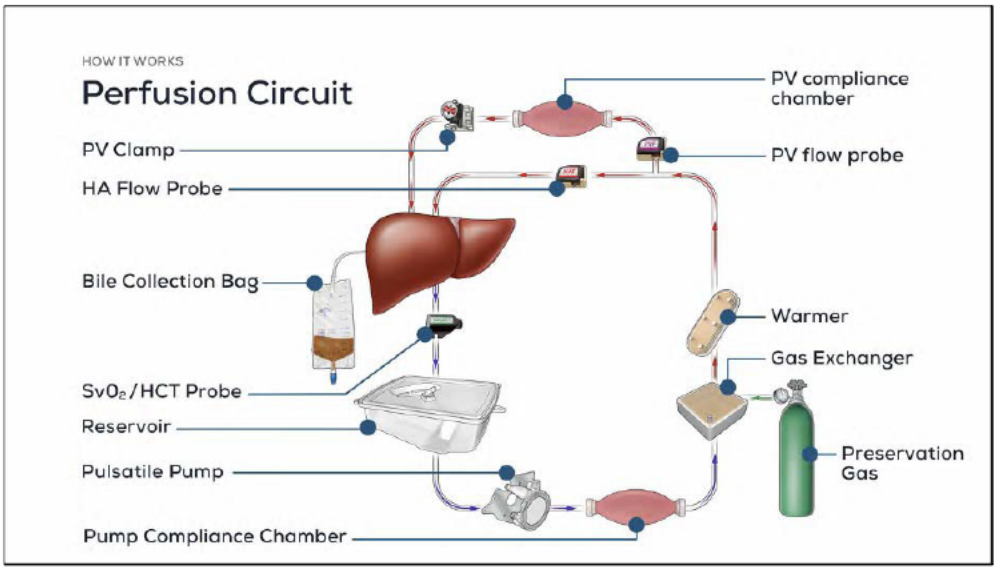
Table 13: Solutions Additives and Perfusate Infusions Supplied by User

	Purpose
Priming Solution/Perfusate Components	
(b)(4)	
Perfusate Additives	
(b)(4)	

	Purpose
(b)(4)	
Infusions to Perfusate (added through SDS infusion*)	
(b)(4)	
*Note that reconstituted OCS Liver Bile Salts are also administered to the organ through the SDS; however, TransMedics provides the OCS Liver Bile Salts.	

Figure 31 below illustrates the circulation of perfusate through the LvPM circuit. The perfusate is pumped from the reservoir by the Circulatory Pump (pulsatile pump as labeled in the figure below) and then directed through the oxygenator. The perfusate then passes through the warmer to reach the desired temperature. The path is then split so that the perfusate is delivered to both the Hepatic Artery (HA) and the Portal Vein (PV). The PV leg of the circuit contains the PV compliance chamber and the PV clamp. The configuration of these two legs of the circuit results in a pulsatile flow of perfusate delivered to the HA and a non-pulsatile flow of perfusate to the PV. Deoxygenated perfusate exits the liver from the Inferior Vena Cava (IVC). The perfusate from the IVC is directed to the reservoir through the drain in the liver chamber. Additionally, the liver circuit directs bile produced by the liver through a bile cannula to a collection bag.

Figure 31: Schematic of OCS Liver System Fluid Flow



To adequately maintain the liver, the OCS Liver System controls and monitors the preservation environment, as shown in Table 14, and as described further below. The user can adjust perfusate flow rate, delivery rate of solutions and additives, gas flow rate, and perfusate temperature within specified ranges. The OCS Liver System calculates and displays pertinent organ status parameters, and provides alarms for parameters out of expected ranges, alarms for low gas, battery and solution capacity, and alarms for sensor failures.

Table 14: Essential Control and Monitoring of the Preservation Environment

Function	Mechanism	Measurement	User Control
Circulate Perfusate	Perfusate Pump	Flow Rate	Pump Flow Rate
		Pressure	
Warm Perfusate	Warmer Plates	Perfusate Temperature	Perfusate 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 Liver System controls rate of perfusate flow circulated through the functioning liver. The OCS contains two 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 configured ranges.

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

Replenish Perfusate: The OCS Liver System oxygenates the perfusate and delivers maintenance solution and bile salts to provide support for the preservation of the liver. The system displays oxygenation saturation values and alerts the user to faults or parameter values outside of specified ranges.

Assess Preservation: The OCS Liver System has been designed to monitor the preservation conditions by measuring flow rates, pressures, and temperatures. The circuit contains ports to draw perfusate 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 Liver 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 Liver 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 Liver System is provided in Appendix 2 of this document.

6. OCS LIVER PROTECT TRIAL

The primary clinical data set supporting this PMA application is the OCS Liver PROTECT trial.

6.1. OCS Liver PROTECT Trial Design and Objectives

The OCS Liver PROTECT trial was a prospective, multi-center, randomized trial of patients randomized 1:1 to the OCS Liver or Control (cold storage). The trial enrolled 300 patients at 20 U.S. liver transplant sites (18 active) between Jan 2016 and Oct 2019. The clinical objective of the trial was to compare the safety and the effectiveness of the OCS Liver System vs. cold storage (Control) to preserve and assess donor livers intended for transplantation that may benefit from warm oxygenated perfusion compared to cold static storage from one or more of the following donor characteristics:

- Donor age ≥ 40 years old; or
- Expected total cross clamp/cold ischemic time ≥ 6 hours; or
- Donor after Cardiac Death (DCD donor) with age ≤ 55 years old; or
- Steatotic liver > 0% and ≤ 40% macrosteatosis at time of retrieval (based on retrieval biopsy readout (only if the donor liver was clinically suspected to be fatty by the retrieval surgeon at time of liver retrieval)).

6.1.1. Primary Effectiveness Endpoint

The Primary Effectiveness Endpoint is the incidence of Early liver Allograft Dysfunction (EAD), defined as the presence of one or more of the following criteria: (1) AST level > 2000 IU/L within the first 7 postoperative days; (2) bilirubin ≥ 10 mg/dL on postoperative day 7; (3) INR ≥ 1.6 on postoperative day 7; or (4) primary non-functioning graft within the first 7 days (defined as irreversible graft dysfunction requiring emergency liver re-transplantation or death, in the absence of immunologic or surgical causes).

6.1.2. Secondary Effectiveness and OCS Donor Liver Assessment Endpoints

- OCS donor liver assessment during perfusion
- Patient survival at day 30 post-transplantation
- Patient survival at initial hospital discharge post liver transplantation.

6.1.3. Other Clinical Endpoints

- Length of initial post-transplant ICU stay

- Length of initial post-transplant hospital stay
- Evidence of ischemic biliary complications diagnosed at 6 and at 12 months
- Extent of reperfusion syndrome as assessed based on the rate of decrease of lactate
- Pathology sample score for liver tissue samples.

6.1.4. Safety Endpoint

The safety endpoint is the incidence of liver graft-related serious adverse events (LGRSAEs) in the first 30 days post liver transplantation, which are defined as:

- primary non-function (defined as irreversible graft dysfunction, requiring emergency liver re-transplantation or death within the first 10 days, in the absence of immunologic or surgical causes);
- ischemic biliary complications (ischemic biliary strictures, and non-anastomotic bile duct leaks);
- vascular complications (liver graft-related coagulopathy, hepatic artery stenosis, hepatic artery thrombosis, and portal vein thrombosis); or
- liver allograft infections (such as liver abscess, cholangitis, etc.).

6.1.5. Trial Population

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

6.1.6. Inclusion Criteria

Donor - At least one of the following:

- Donor age ≥40 years old; or
- Expected total cross clamp/cold ischemic time ≥6 hours; or
- Donor after circulatory death (DCD) with age ≤55 years old; or
- Steatotic liver >0% and ≤40% macrosteatosis at time of retrieval (based on retrieval biopsy readout only if the donor liver was clinically suspected to be fatty by the retrieval surgeon at time of liver retrieval)

Recipient - Day of Transplant - Recipients were required to meet all the following criteria on the day of transplant:

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

6.1.7. Exclusion Criteria

Donor - At least one of the following:

- Living donors
- Liver intended for split transplants
- Positive serology (HIV, Hepatitis B surface antigen & C)
- Presence of moderate or severe traumatic liver injury, or anatomical liver abnormalities that would compromise ex- vivo preservation of the donor liver (i.e., accessory blood vessels or other abnormal anatomy that require surgical repair) and livers with active bleeding (e.g., hematomas)
- Donor livers with macrosteatosis of > 40% based on retrieval biopsy readout.

Recipient - Day of Transplant - Recipients were excluded if they met any of the following criteria on the day of transplant:

- Acute, fulminant liver failure
- Prior solid organ or bone marrow transplant
- Chronic use of hemodialysis or diagnosis of chronic renal failure, defined as chronic serum creatinine of >3 mg/dl for >2 weeks and/or requiring hemodialysis
- Multi-organ transplant
- Ventilator dependent
- Dependent on >1 IV inotropic support to maintain hemodynamics.

6.1.8. Analysis Populations

The primary analysis population was pre-specified as the Per Protocol (PP) population which consists of all randomized patients who were transplanted and had no major protocol violations and for whom the donor liver received the complete preservation procedure as per the randomization assignment. In the PP analyses, patients were analyzed in the groups to which they were randomized. The primary analysis of the primary and secondary effectiveness endpoints, and of other endpoints are based on the PP population.

The Modified Intent-to-treat (mITT) population consists of all randomized patients who were transplanted in the trial. In the mITT Population, patients were analyzed as randomized. The mITT analyses are the secondary analyses of effectiveness.

The As Treated (AT) population consists of all treated patients, i.e., all patients who were transplanted in the trial with a donor liver preserved with either OCS or Control. In analyses based on this population, patients were analyzed as treated. Analyses of safety endpoints are performed based on the AT population.

6.1.9. Statistical Analyses

6.1.9.1. Randomization

After confirmation of eligibility, obtaining informed consent, and a matching donor liver is identified, potential liver transplant recipients were randomized 1:1 to have their donor livers preserved using either the OCS Liver perfusion or the standard cold static preservation technique (Control) using cold flush and storage. Randomization was performed through the

Interactive Web Response System (IWRS). Patients who were not transplanted with the matching donor liver were re-randomized and treated as a new patient.

6.1.9.2. Sample Size

The sample size for this trial was determined based on the effectiveness endpoint, Early Liver Allograft Dysfunction (EAD) in the first 7 days post liver transplantation. The sample size calculation assumed a non-inferiority test, based on the upper bound of the Exact unconditional one-sided confidence interval for the difference in proportions using the Farrington and Manning score statistic, an alpha level of 0.05, a non-inferiority margin of 0.075, a 1:1 allocation, true proportions for the primary effectiveness endpoint of 0.2 for the OCS treatment and 0.25 for the Control treatment, and power of 80%. Based on these specifications, the required sample size was determined to be 144 transplanted recipients per treatment group, or 288 total transplanted patients. To ensure an adequate number of patients in the Per Protocol Population, the sample size was increased to a total of 300 transplanted patients.

6.1.9.3. Statistical Analyses – Effectiveness

The primary hypothesis for this trial is that the OCS treatment is non-inferior to the standard of care treatment with respect to the primary effectiveness endpoint. The non-inferiority margin δ is taken to be 0.075. If non-inferiority was demonstrated using a significance level of 0.05, a two-sided test of superiority was to be performed.

The primary effectiveness endpoint was analyzed by calculating, for each treatment group, the sample proportion of patients meeting the primary effectiveness endpoint, as well as an exact (Clopper-Pearson) 95% confidence interval for the corresponding population proportion. The 95% upper bound of the exact unconditional one-sided confidence interval based on the Farrington and Manning score statistic was calculated for the difference between the two population proportions (OCS – Control). An upper confidence limit less than $\delta = 0.075$ resulted in rejection of the null hypothesis in favor of the alternative hypothesis and the demonstration of non-inferiority of OCS to Control for the primary effectiveness endpoint. In the event non-inferiority was demonstrated, Fisher's exact test (two-sided) would be used to test for superiority.

This endpoint was analyzed using the Per Protocol and mITT Populations. The Per Protocol analysis was considered the primary analysis. Multiple imputation methods were used for data imputation for any patients with missing values for this endpoint.

The secondary effectiveness and OCS donor liver assessment endpoints for this trial, listed in the order in which they were tested using the fixed sequence testing procedure (shown in Figure 5), were as follows:

- OCS Measurements during organ perfusion
- Patient survival at day-30 post-transplantation
- Patient survival at initial hospital discharge post liver transplantation.

The hypothesis for the endpoint of OCS donor liver assessment during perfusion was that, among donor livers preserved using OCS for the entire preservation period, the proportion of livers on which measurements of lactate level, average bile production rate, Hepatic Artery and

Portal Vein Pressure during perfusion are available on OCS device before transplant was at least 85%. This endpoint was analyzed by calculating the sample proportion of donor livers meeting the endpoint, as well as an exact 95% one-sided lower confidence bound for the corresponding population proportion. A lower confidence bound greater than 0.85 resulted in the demonstration that the true proportion is greater than 0.85 for the OCS donor liver assessment endpoint.

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. The secondary effectiveness endpoints will be analyzed using the PP and the mITT Populations. The Per Protocol analysis will be considered the primary analysis.

The primary hypothesis for the first secondary effectiveness endpoint is that the OCS treatment is non-inferior to the standard of care treatment. The non-inferiority margin is taken to be 0.075. This endpoint was analyzed by calculating the 95% upper confidence limit based on the normal approximation for the difference between the two population proportions (Control - OCS). An upper confidence limit less than $\delta = 0.075$ will result in rejection of the null hypothesis in favor of the alternative hypothesis and demonstration of non-inferiority of OCS to Control. In the event non-inferiority was demonstrated, Fisher's exact test (two-sided) will be used to test for superiority.

The second secondary effectiveness endpoint, patient survival at initial hospital discharge post liver transplantation, was analyzed in a manner analogous to the first secondary effectiveness endpoint with the same non-inferiority margin of 0.075.

Because fixed sequence testing was used for the secondary endpoints, no adjustment for the multiplicity of these endpoints needed to be made.

These endpoints were analyzed using the Per Protocol and mITT Populations, with the Per Protocol analysis being considered the primary analysis. Multiple imputation methods were to be used for data imputation for patients with missing values for these endpoints.

6.1.9.4. Statistical Analyses – Safety

Safety was analyzed by examination of the frequency of liver graft-related serious adverse events (LGRSAEs) up to the 30-day follow-up after transplantation.

This endpoint was summarized by treatment group using descriptive statistics. For each treatment group, a 95% confidence interval for the mean based on the t-distribution and a 95% confidence interval based on the t-distribution for the difference in means between the two treatments was calculated.

For the number of liver graft-related SAEs, the hypothesis is that the OCS treatment is non-inferior to the standard of care treatment. The non-inferiority margin is taken to be 1.00. The safety endpoint was analyzed using a one-sided, two-sample t-test with an alpha level of 0.05. If non-inferiority was demonstrated, a corresponding (two-sided) test of superiority will be performed. This endpoint was analyzed based on the As Treated Population.

Since this endpoint is independent of the primary and secondary effectiveness endpoints, and since the PROTECT trial was designed to show both safety and effectiveness, no multiplicity adjustment was necessary for the safety endpoint.

6.2. Investigators and Study Administrative Structure

The study administrative structure and DSMB members are shown in Table 15 and the Clinical Events Committee (CEC) members are shown in Table 16. The CEC consisted of three members who are experts in transplant surgery and hepatology.

Table 15: Study Administrative Structure - Oversight Personnel

Function	Name	Role/Affiliation
Product Director	(b)(6)	Sponsor/TransMedics, Inc.
VP, Clinical Affairs	(b)(6)	Sponsor/TransMedics, Inc.
VP, Global Regulatory Affairs	(b)(6)	Sponsor/TransMedics, Inc.
Statistical Consultant	(b)(6)	Independent Biostatisticians (b)(6)
Data Safety Monitoring Board	(b)(6)	Chairperson (b)(6)
	(b)(6)	Biostatistician (b)(6)
	(b)(6)	Gastroenterology and Hepatology (b)(6)

Table 16: Clinical Events Committee Members

Name	Hospital Affiliation	Specialty
(b)(6)		Transplant surgery
(b)(6)		Transplant surgery
(b)(6) (b)(6))	(b)(6) (b)(6)	Gastroenterology and Hepatology Transplant Surgery

An Independent Core Pathology Laboratory reviewed all liver biopsy samples, including for the turned down donor livers. Table 17 below identifies the Core Pathology Laboratory and independent pathologist.

Table 17: Independent Core Pathology Laboratory

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

The investigational sites, PIs, and trial enrollment are shown in Table 18 below.

Table 18: Study Sites, Principal Investigators (PIs) and Enrollment (As Treated, not as randomized)

Site ID	PI Name	Site Name	OCS	Control	Total
LV-01	(b)(6)		33	37	70
LV-02	(b)(6)		23	23	46
LV-03	(b)(6)		4	1	5
LV-04	(b)(6)		25	19*	44
LV-05	(b)(6)		2	3	5
LV-06	(b)(6)		23	25	48
LV-07	(b)(6)		2	3	5
LV-08	(b)(6)		3	3	6
LV-09	(b)(6)		11	8	19
LV-10	(b)(6)		5	7	12
LV-11	(b)(6)		4	3	7
LV-12	(b)(6)		1	3	4

Site ID	PI Name	Site Name	OCS	Control	Total
LV-13	(b)(6)		5	2	7
LV-14	(b)(6)		5	4	9
LV-15	(b)(6)		3	1	4
LV-17	(b)(6)		1	0	1
LV-19	(b)(6)		0	1	1
LV-20	(b)(6)		3	4	7
			153	147	300

*Includes Patient (b)(6) who died in the OR prior to receiving the transplant.

6.3. Trial Course Complexities and Terminology

This section describes the trial course complexities and terminology.

6.3.1. Randomization and Re-randomization:

The OCS Liver PROTECT trial is a randomized trial of liver transplant recipients who were transplanted with donor livers that were preserved using either OCS Liver perfusion (OCS) or Cold static storage (Control). Randomized trials in the field of organ preservation for transplantation are uniquely complex due to the multi-factorial and complex nature of the organ allocation and retrieval process. Importantly, given that the OCS Liver PROTECT trial was targeting DBD and DCD donors with multiple risk factors, the PROTECT trial included a pre-specified re-randomization procedure.

Patients who were randomized and were matched to a donor organ that was subsequently not accepted for transplant (i.e., a dry run) lost this randomization assignment and went back to the pool of candidates awaiting another donor assignment and another randomization. This procedure minimized any impact of potential clinical bias when evaluating and accepting high risk donor livers.

Randomization occurred at the recipient's site, at the time of initial organ match, prior to dispatching the procurement team to the donor site for physical assessment of the donor liver and retrieval. Randomization was not possible at the donor's site after physical assessment of the donor liver due to the team logistics and preparation needed for OCS preservation, which involves additional technology, blood products, and associated solutions.

6.3.2. Rejected for Transplant in Donor Body after Randomization (Dry Run)

At final physical assessment of the donor liver in the donor abdomen prior to retrieval, the organ may be deemed to be unsuitable for transplantation based on the clinical assessment of the procurement surgeon and may be declined for transplant all together regardless of the method of preservation. This results in a "dry run." This dry run situation is common in solid organ transplantation, and it occurs in 20 to 25% of donor retrievals (Israni, et al., 2020). In this situation where the procurement team has traveled to the donor organ site, and has assessed the organ and declined it, the team returns to the recipient site without an organ. The intended recipient in these cases remained in the OCS Liver PROTECT trial, awaiting another donor match and another randomization.

6.3.3. Rejected after Assessment on OCS Liver System (Turndown)

When a donor organ is placed on the OCS, it is continually assessed during perfusion to ensure the organ suitability for transplant. In some cases, rising lactate levels or other unfavorable parameters resulted in these organs being deemed not suitable for transplant. These are considered "turndown" organs and the intended recipient in these cases remained in the OCS Liver PROTECT trial, awaiting another donor match and another randomization.

6.3.4. Transplanted Off Study after Randomization using Cold Storage

If a randomized recipient was matched with a donor organ that was expected to meet the inclusion/exclusion criteria but, upon assessment in the donor, the donor organ did not meet all of the pre-specified trial inclusion/exclusion criteria, then the randomized recipient was withdrawn from the trial and received the organ procured via standard of care (cold storage, on ice) as it would have been unethical to do otherwise and waste the liver allograft. An example of this is the presence of accessory vessels in the donor organ (a donor liver exclusion criteria), as these livers cannot be instrumented on the OCS Liver System without performing vascular reconstruction in the donor OR.

In some cases, a randomized recipient was matched with a donor organ that was expected to meet the inclusion/exclusion criteria, but due to logistical or other reasons the team was not able to retrieve the organ perfused on the OCS. In these cases, the randomized recipient was withdrawn from the trial and received the organ procured via standard of care (cold storage, on ice) as it would have been unethical to do otherwise and waste the liver allograft.

6.3.5. Transplanted Off Study without active Randomization assignment

If a recipient was matched to a donor liver, and that donor organ did not meet trial criteria but the surgeon found the organ acceptable for transplant, the investigator did not re-randomize the recipient and he/she was withdrawn from the OCS Liver PROTECT trial and was transplanted outside of the trial without a randomization assignment as it would have been unethical to do otherwise and waste the liver allograft.

6.3.6. Patient Delisted for Transplant, Died, or Withdrew Consent

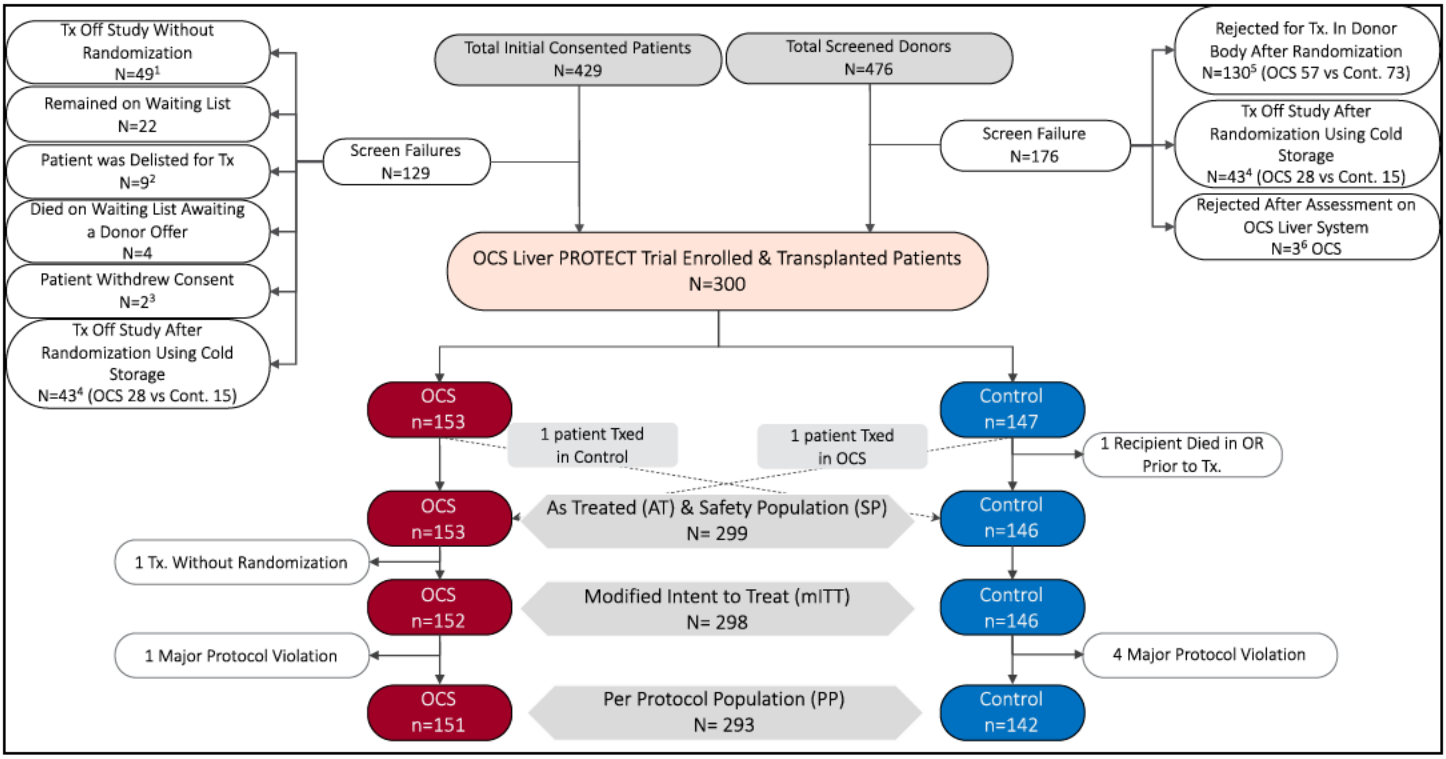
In some cases, the recipient's health status deteriorated while on the waiting list for a potential donor liver. In these cases, the patient was delisted from the transplant waiting list or, in some cases, the patient died on the waiting list while waiting for a potential donor liver offer.

In some cases, patients withdrew consent and did not receive a randomized donor liver in the OCS Liver PROTECT trial.

6.4. Patient Accountability

The consort diagram (Figure 32) summarizes the trial enrollment. The footnotes that follow describe the patient groupings and events.

Figure 32: Enrollment Consort Diagram



[1] Transplanted (Tx) Off Study without active Randomization Assignment After Initial Donor Offer(s) were Declined for Tx at Retrieval (N=49):

- N=25 – Subsequent donor liver offer did not meet OCS Liver PROTECT trial inclusion criteria.
- N=21 – Site PI decided not to re-randomize patients at donor offer due to donor operating room (OR) logistical reasons or lack of trial trained retrieval staff at time of donor offer.
- N=3 – Patients no longer met trial eligibility criteria due to deteriorating health status or received split liver transplant.

[2] Patient was Delisted for Tx (N=9: 6 OCS, 3 Control):

- N= 3 (2 OCS, 1 Control) – Metastatic cancer discovered at recipient surgical exploration.
- N= 4 (2 OCS, 2 Control) – Delisted for transplantation due to deteriorating health status.
- N= 2 (2 OCS, 0 Control) – Deemed ineligible for trial by site PI and was withdrawn.

[3] Patients Withdrew Consent for Trial (N=2: 1 OCS, 1 Control)

[4] Tx Off Study After Randomization Using Cold Storage (N=43: 28 OCS, 15 Control):

- N= 39 (24 OCS, 15 Control) – Donor liver did not meet eligibility due to the presence of accessory vessels, liver hematoma or required surgical vascular repair.
- N= 4 (4 OCS, 0 Control) – Logistical reasons, including:
  - Donor family not consenting to research (requirement of organ procurement organizations);
  - Unable to obtain pre-retrieval liver biopsy;
  - OPO delaying OR time resulting in trained trial retrieval team being off call; and
  - Recipient deterioration with renal insufficiency on day of transplant.

[5] Rejected for Tx in Donor Body After Randomization (N=130: 57 OCS, 73 Control):

- N=42 (18 OCS, 24 Control) – DCD donor did not expire within 30 mins.
- N=31 (9 OCS, 22 Control) – Clinical judgement at retrieval.
- N=27 (13 OCS, 14 Control) – Steatosis.
- N=9 (3 OCS, 6 Control) – Cirrhosis or fibrosis of the donor liver.

- N=4 (2 OCS, 2 Control) – Vasculature abnormalities or diseased.
- N=3 (3OCS, 0 Control) – Donor-recipient organ size mismatch.
- N=2 (2 OCS, 0 Control) – Liver or Kidney malignancy discovered during retrieval.
- N=12 (7 OCS, 5 Control) – Other reasons: re-allocation, donor did not progress or logistical reasons.

[6] DCD Donors Rejected for Tx After OCS Liver Assessment N=3

- N=2 – Rising lactate levels despite maximizing OCS Liver perfusion parameters.
- N=1 – Donor liver pre-retrieval biopsy revealed extensive bridging fibrosis.

OCS Liver PROTECT Trial Patients: Three hundred (300) patients were consented, randomized, and considered enrolled after meeting all trial eligibility criteria and after the transplant surgery was initiated.

Recipient Died in OR Prior to Transplant: One patient (b)(6) who was randomized to Control, died in the operating room after skin incision but prior to receiving the transplant.

Treated Differently than Randomized – Treatment Cross Over: Two (2) patients were treated differently than randomized:

- Patient (b)(6) was randomized to Control, but was treated with OCS, due to receiving a liver preserved on OCS that was intended for Patient (b)(6). Patient (b)(6) randomized to OCS, was found to have metastatic cancer at the time of transplant. The local OPO reallocated the organ to Patient (b)(6) who had been randomized to Control. Patient (b)(6) transplant is captured as a major protocol violation.
- Patient (b)(6) was randomized to OCS but was preserved on cold storage due to an OCS device malfunction prior to organ instrumentation. This patient and event are captured as a major protocol violation and this event is also detailed in the malfunction section of this report.

Transplanted without Randomization: Patient (b)(6) was transplanted without randomization after receiving a liver preserved on OCS that was intended for Patient (b)(6) Patient (b)(6) was found to have metastatic cancer at the time of transplant. The local OPO reallocated the liver allograft to Patient (b)(6) who had been consented for the trial but was not randomized.

Major Protocol Violations: Five (5) protocol deviations (1 OCS and 4 Control) were categorized by the Clinical Events Committee as major protocol violations and are listed in Table 19 below.

Table 19: Summary of Major Protocol Violations

Randomization Assignment	Patient Number	Deviation Type	Description
OCS	(b)(6)	Patient randomized to OCS, but organ preserved on cold storage	Patient was randomized to OCS but organ was preserved on cold storage due to device malfunction prior to organ instrumentation. The patient was successfully transplanted. A description of the device malfunction is as follows: During setup of the system at the donor site, the system displayed the message "Perfusion Module Not Present" even though the Liver Perfusion Module was installed. Despite attempts

Randomization Assignment	Patient Number	Deviation Type	Description
			to reinstall the module, it was not recognized as being installed in the system.
Control	(b)(6)	Patient randomized to Control but received OCS preserved organ	This patient received a liver preserved on the OCS that was originally intended for another Patient, (b)(6) Patient (b)(6) was found to have metastatic cancer at the time of transplant surgery and the transplant procedure was aborted. The local OPO reallocated the organ to Patient (b)(6) Although Patient (b)(6) was randomized to Control, the Patient received the organ being maintained on OCS. The patient was successfully transplanted.
Control	(b)(6)	Donor Eligibility Criteria	The donor organ for this patient was noted to have accessory vessels post-transplantation upon operative report review.
Control	(b)(6)	Donor Eligibility Criteria	The donor organ for this patient was noted to have accessory vessels post-transplantation upon operative report review.
Control	(b)(6)	Donor Eligibility Criteria	The donor organ for this patient was noted to have accessory vessels post-transplantation upon operative report review.

6.5. Analysis Populations

Based on the above definitions, the OCS Liver PROTECT trial analysis populations are shown in Figure 33 and Table 20 below.

Figure 33: OCS Liver PROTECT Trial Analysis Populations

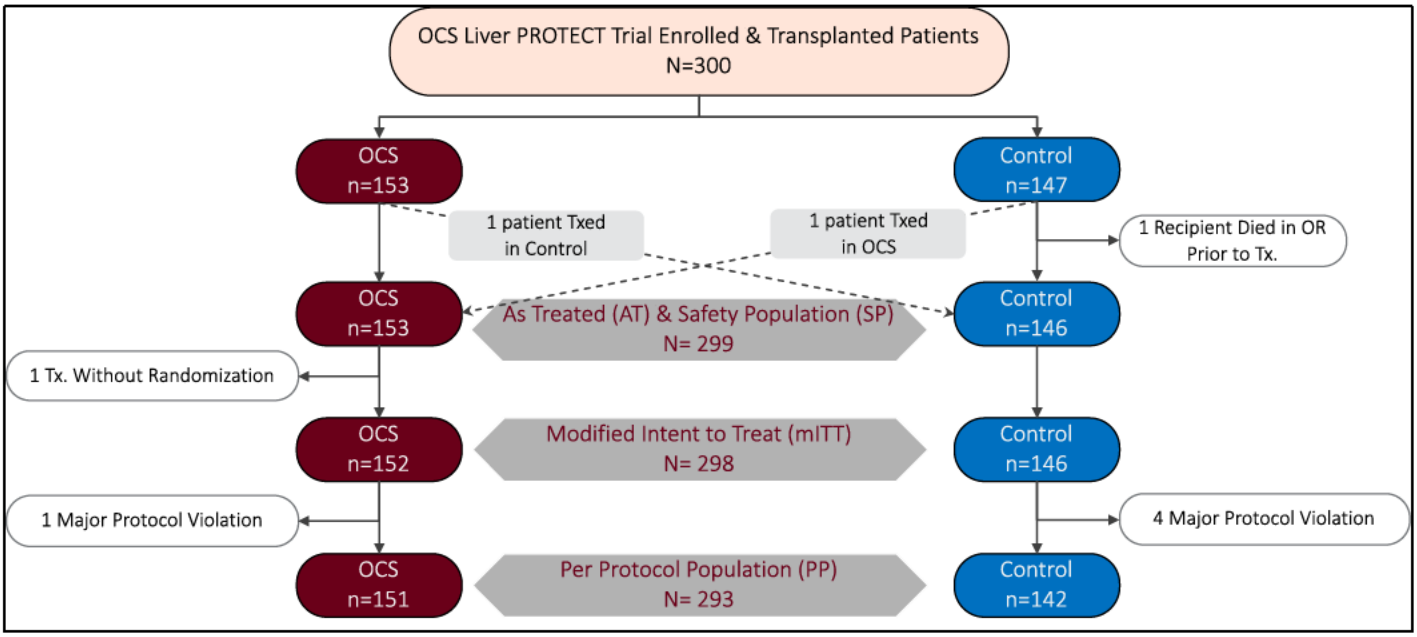


Table 20: Analysis Populations

Population	Analyzed By	Major Protocol Violation	Total Number Patients
As-Treated (AT)	Treatment received regardless of random assignment	Included	299 (153 OCS, 146 Control)
Modified Intent-to-Treat (mITT)	Randomized assignment regardless of treatment	Included	298 (152 OCS, 146 Control)
Per Protocol (PP)	Randomized assignment regardless of treatment, excluding major protocol violations	Not Included	293 (151 OCS, 142 Control)

6.6. Donor Liver Population

The Donor Liver Population consists of all donor livers for which the potential recipient was randomized, and for which preservation had been initiated using either OCS or Control. Table 21 below shows the accountability of the donor livers in this trial for each randomized group.

Table 21: Donor Liver Accountability

	OCS	Control	Total
Screened Donor Livers	240	235	475[1]
Dry Runs	57	73	130
Transplanted off-trial using cold storage after randomization (screen failures)	28	15	43
Randomized donor liver population in PROTECT	155	147	302
Liver Randomized but not Transplanted	3[2]	1[3]	4
Donor Liver Transplanted (mITT population)	152	146	298

(1) Does not include 1 donor liver for recipient (b)(6), who was treated with OCS without randomization.
(2) 3 organs instrumented on OCS were turndowns.
(3) Patient (b)(6) was not transplanted due to death in OR prior to transplantation.

6.7. Recipient Characteristics

The recipient demographics and baseline characteristics are shown in Table 24. The majority of the recipients were males (66-69%), with a mean age of 57-58 years and a mean MELD score of 28. Almost a third of the recipients had a history of diabetes and the most prevalent primary diagnosis was alcoholic cirrhosis. The two treatment groups were similar in all demographic and baseline characteristics with no significant differences noted.

Table 22: Recipient Demographic and Baseline Characteristics (AT Population)

Parameter	OCS (N=153)	Control (N=146)
Recipient Age (yrs): mean ± SD	57.07 ± 10.33	58.59 ± 10.04

Parameter	OCS (N=153)	Control (N=146)
Gender		
• Male	102 (66.7%)	100 (68.5%)
• Female	51 (33.3%)	46 (31.5%)
BMI (kg/m^2): mean ± SD	29.67 ± 5.38	29.51 ± 5.51
MELD Score: mean ± SD Median	28.4 ± 6.90 29.0	28.0 ± 5.71 29.0
History of diabetes	44 (28.8%)	44 (30.1%)
History of liver cancer	60 (39.2%)	63 (43.2%)
Primary diagnosis		
• Cholestatic Diseases	9 (5.9%)	8 (5.5%)
• Chronic Hepatitis	27 (17.6%)	36 (24.7%)
• Alcoholic Cirrhosis	54 (35.3%)	48 (32.9%)
• Metabolic Diseases	6 (3.9%)	6 (4.1%)
• Primary Hepatic Tumors	14 (9.2%)	15 (10.3%)
• NASH	24 (15.7%)	20 (13.7%)
• Other	19 (12.4%)	13 (8.9%)

6.8. Donor Characteristics

The donor demographics and baseline characteristics are shown in Table 23. The donor organs used in this trial were associated with some clinical risk factors that may make them less likely to be used for transplantation due to the limitation of cold ischemic storage, e.g., donors with advanced age, multiple co-morbidities like steatosis, long cross-clamp time, or donation after circulatory death (DCD). In fact, ~60% of the donor livers in the study met more than one of these donor characteristics. Both donor groups were similar in risk factors of age ≥ 40 years, cross clamp time > 6 hours and macrosteatosis; however, the OCS arm included substantially more DCD donors. DCD liver transplantation is considered to be associated with higher clinical risks due to the impact of warm ischemic injury of the agonal phase on the incidence of EAD and ischemic biliary complications post-transplant (Mateo, et al., 2006; Mathur, et al., 2010, Lee et al., 2014).

Table 23: Donor Demographic and Baseline Characteristics (AT Population)

Parameter	OCS (N=152 [2])	Control (N=146)
Donor Age (years): mean ± SD	45.84 ± 14.90	46.96 ± 15.22
Cause of death		
• Cerebrovascular Hemorrhage	44 (28.9%)	50 (34.2%)

Parameter	OCS (N=152 [2])	Control (N=146)
• Head trauma	35 (23.0%)	29 (19.9%)
• Cardiac	13 (8.6%)	10 (6.8%)
• Other (Anoxia, CSF infection, Suicide, Stroke)	60 (39.5%)	57 (39.0%)
Donor Characteristics [1]		
• ≥ 40 years old	102 (67.1%)	93 (63.7%)
• Total cross clamp ≥ 6 hours	48 (31.6%)	56 (38.4%)
• DCD ≤ 55 years old	28 (18.4%)	13 (8.9%)
• Steatotic liver > 0% and ≤ 40% macrosteatosis at time of retrieval	95 (62.5%)	86 (58.9%)
• Multiple Donor Characteristics	95 (62.5%)	85 (58.2%)

(1) Multiple donor characteristics (inclusion criteria) could be met (total 60.4% of all donors).
(2) Does not include donor organ for Patient (b)(6), as this patient was not randomized.

6.9. Donor Liver Function Tests and Preservation Characteristics

At the time of organ acceptance, the donor liver function tests were similar between the two groups as shown in Table 24 below.

Table 24: Donor Liver Function Tests at Donor Acceptance (AT Population)

Parameter	OCS (N=152)[1]	Control (N=146)
Bilirubin Levels (mg/dL)	152	145
Mean ± SD	0.756 ± 0.5720	0.732 ± 0.6728
Median	0.600	0.500
Minimum - Maximum	0.20 - 3.70	0.10 - 6.10
AST (U/L)	152	146
Mean ± SD	85.7 ± 93.14	82.0 ± 100.64
Median	56.0	44.0
Minimum - Maximum	12 - 562	9 - 529
ALT (U/L)	152	146
Mean ± SD	74.8 ± 106.78	91.5 ± 207.47
Median	41.0	38.5
Minimum - Maximum	6 - 976	7 - 2198

Parameter	OCS (N=152)[1]	Control (N=146)
GGT (U/L)	82	69
Mean ± SD	62.9 ± 54.87	69.3 ± 81.09
Median	45.0	56.0
Minimum - Maximum	10 - 295	7 - 578
Alkaline Phosphatase (U/L)	152	145
Mean ± SD	83.9 ± 49.60	88.7 ± 61.77
Median	72.5	76.0
Minimum - Maximum	29 - 513	28 - 533
INR	150	142
Mean ± SD	1.257 ± 0.2319	1.376 ± 1.1896
Median	1.200	1.225
Minimum - Maximum	0.80 - 2.59	0.90 - 15.10
Final Donor Arterial Lactate Level (mmol/L)	87	47
Mean ± SD	1.752 ± 1.8103	1.622 ± 1.0236
Median	1.350	1.400
Minimum - Maximum	0.16 - 13.63	0.10 - 4.80
(1) Does not include donor organ for Patient (b)(6) as this patient was not randomized.		

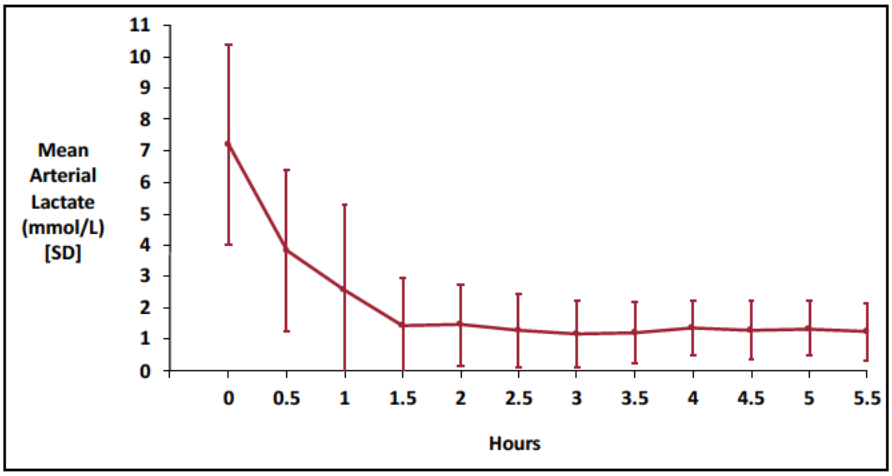
Donor livers were perfused on OCS and were maintained in a near physiologic condition based on OCS perfusion parameters, bile production, and blood gas results of the perfusate (Table 27 below). Importantly, the OCS Liver lactate trend showed a steadily declining and stable trend throughout perfusion indicating that the donor liver has recovered (i.e., been resuscitated) from the non-physiologic insult of organ donation and procurement to a metabolically active normal liver function. (Figure 11).

Table 25: OCS Liver Perfusion Parameters and Perfusate Chemistry Levels

OCS Perfusion Parameters and Perfusate Chemistry	OCS (N=152)
OCS Liver Perfusion Time (mins) mean ± SD	276.6 ± 117.4
Hepatic Artery Pressure (mmHg) - mean ± SD	70.6 ± 16.2
Hepatic Artery Flow (L/min) - mean ± SD	0.7 ± 0.2
Portal Vein Pressure (mmHg) - mean ± SD	5.4 ± 2.3
Portal Vein Flow (L/min) - mean ± SD	1.3 ± 0.1
Total Bile Production (ml) - mean ± SD	28.3 ± 15.9

OCS Perfusion Parameters and Perfusate Chemistry	OCS (N=152)
pH- mean ± SD	7.43 ± 0.1
PaO_2 (mmHg) mean ± SD	420.2 ± 80.7
PCO_2 (mmHg) mean ± SD	41.5 ± 14.6
HCO_3 (mmHg) mean ± SD	28.6 ± 10.3

Figure 34: OCS Liver Perfusion Lactate Trend for Transplanted Livers in PROTECT Trial

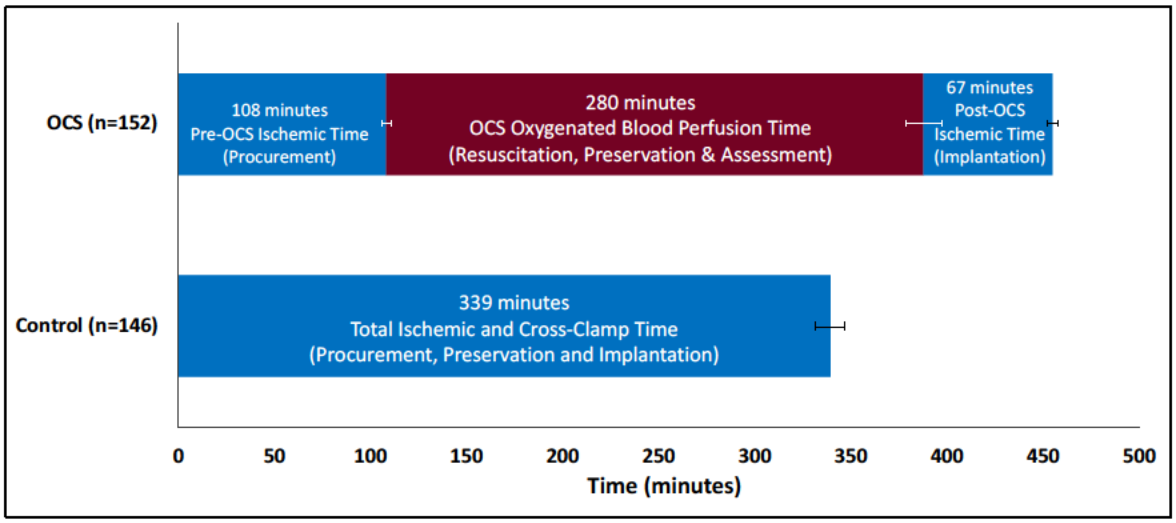


The use of OCS Liver System altered the nature of the critical time from removal from the donor body to reimplantation into the recipient (i.e., total out of body or cross-clamp time). The use of the OCS Liver System significantly reduced the total cold ischemic time on the liver allografts by limiting the ischemic times to 2 obligatory time periods:

- **Pre-OCS Ischemic Time:** This is the time needed to surgically remove the donor liver from the body of the donor, perform the back table surgical preparation of the liver to be perfused on OCS and instrument it on the OCS Liver System. The OCS instrumentation takes ~10-15 mins;
- **Post-OCS Ischemic Time:** this is the time needed to surgically reimplant the liver allograft into the recipient.

Otherwise, throughout the OCS perfusion, the conditions for the donor liver allograft were not ischemic given that it was perfused on OCS with warm, oxygenated blood perfusate until it was ready to be transplanted. On the other hand, Control liver allografts were ischemic from the time they were procured from the donor body until they were implanted into the recipient. Figure 35 below demonstrates these critical time windows.

Figure 35: Overall Out of Body Times in PROTECT Trial (AT Population)



Based on the above unique characteristics of the OCS, the injurious total ischemic time was significantly reduced on the OCS Liver System compared to Control, despite the OCS having significantly longer total cross-clamp (out of body) time Figure 36 below).

Figure 36: Total Cross-Clamp and Ischemic Times for OCS vs. Control Arms (AT Population)

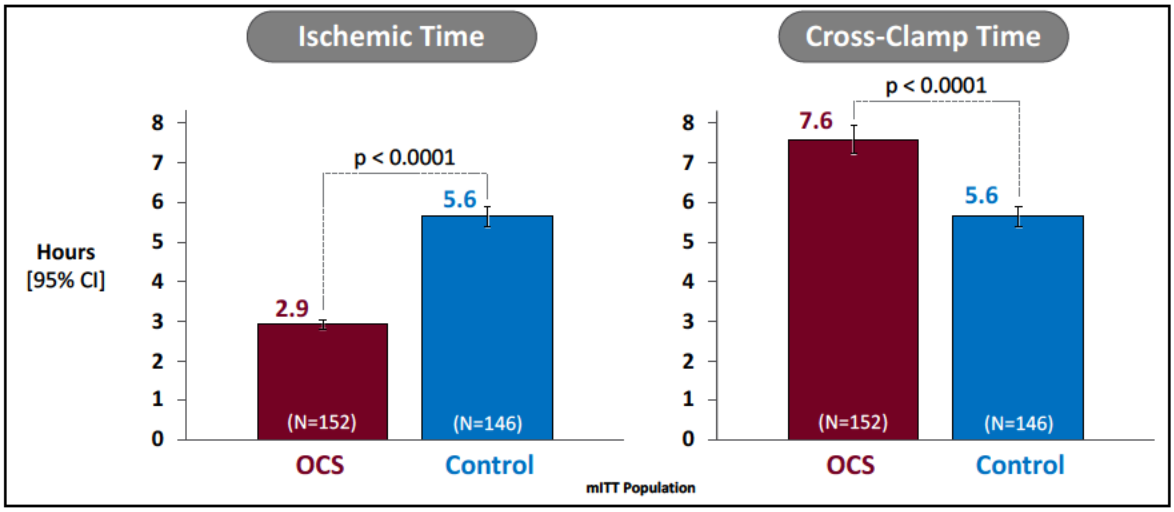


Table 26 below provides the liver perfusion parameters for the OCS preserved organs.

Table 26: Donor Liver OCS Perfusion Parameters (AT Population)[1]

Parameter	OCS (N=152)
Pump Flow (L/min)	152
Mean ± SD	1.947 ± 0.2038
Median	1.957
Minimum - Maximum	1.19 - 2.39
Hepatic Artery Pressure Mean (mmHg)	152
Mean ± SD	70.6 ± 16.19

Parameter	OCS (N=152)
Median	70.4
Minimum - Maximum	33 - 104
Hepatic Artery Flow (L/min)	152
Mean ± SD	0.654 ± 0.1479
Median	0.686
Minimum - Maximum	0.16 - 0.91
Portal Vein Pressure Mean (mmHg)	152
Mean ± SD	5.4 ± 2.26
Median	5.1
Minimum - Maximum	1 - 14
Portal Vein Flow (L/min)	152
Mean ± SD	1.293 ± 0.1496
Median	1.292
Minimum - Maximum	0.81 - 1.65
(1) Does not include donor organ for Patient (b)(6) , as this patient was not randomized	

6.10. Donor Liver Clinical Turndown After Assessment on OCS Liver System

Given that the OCS Liver System enabled assessment of the donor livers ex-vivo, there were 3 DCD donor livers that were preserved and assessed on the OCS Liver System and were clinically turned down for transplantation due to rising lactate while being perfused on OCS Liver System in 2 cases and due to pre-retrieval pathology results in the third case. These 3 cases are described below:

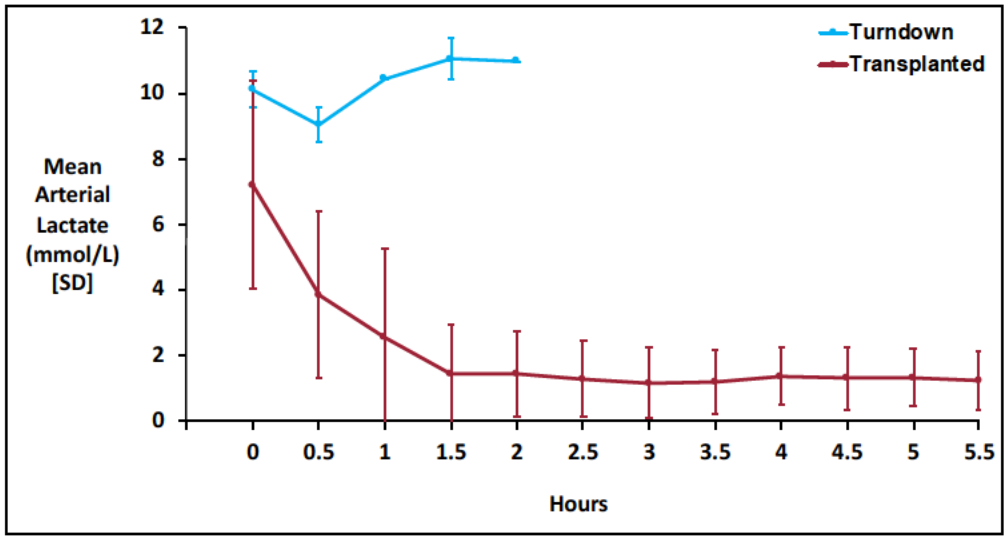
- **Patient 1** (b)(6) **:** was randomized to OCS. The donor liver was perfused on the OCS for 1 hour and 42 minutes and was not accepted for transplantation due to the clinical decision by the accepting transplant surgeon due to pre-retrieval pathology results of widespread bridging fibrosis of the donor liver that was also confirmed by the accepting center's pathologist. The intended recipient remained in the study and was later transplanted with a liver preserved on OCS and is included in the PROTECT trial. The patient did not experience EAD and was alive at Day 366 with no graft failure.
- **Patient 2** (b)(6) **):** was randomized to OCS. The donor liver was perfused on the OCS for 2 hours and 46 minutes and was not utilized due to rising lactate levels while on OCS despite multiple attempts to maximize OCS Liver perfusion parameters. The starting lactate of 10.08 mmol/L and ending lactate of 10.98 mmol/L (see Figure 37 below). The core pathology lab examination revealed widespread hepatocyte cytoaggregation combined with early hepatocyte necrosis. The intended recipient

remained in the study on the waiting list waiting for an organ match until PROTECT enrollment completion and was not transplanted in the study.

- **Patient 3** (b)(6) **:** was randomized to OCS. The donor liver was perfused on the OCS for 2 hours and 38 minutes and was not utilized due to rising lactate levels despite multiple attempts to maximize OCS Liver perfusion parameters. The starting lactate of 9.19 mmol/L and ending lactate of 10.25 mmol/L (see Figure 37 below). The core pathology lab examination revealed significant widespread hepatocyte cytoaggregation combined with early hepatocyte necrosis. The intended recipient remained in the study and was later re-randomized and transplanted in the PROTECT trial in the Control arm. The patient experienced EAD and was alive at Day 353 with no graft failure.

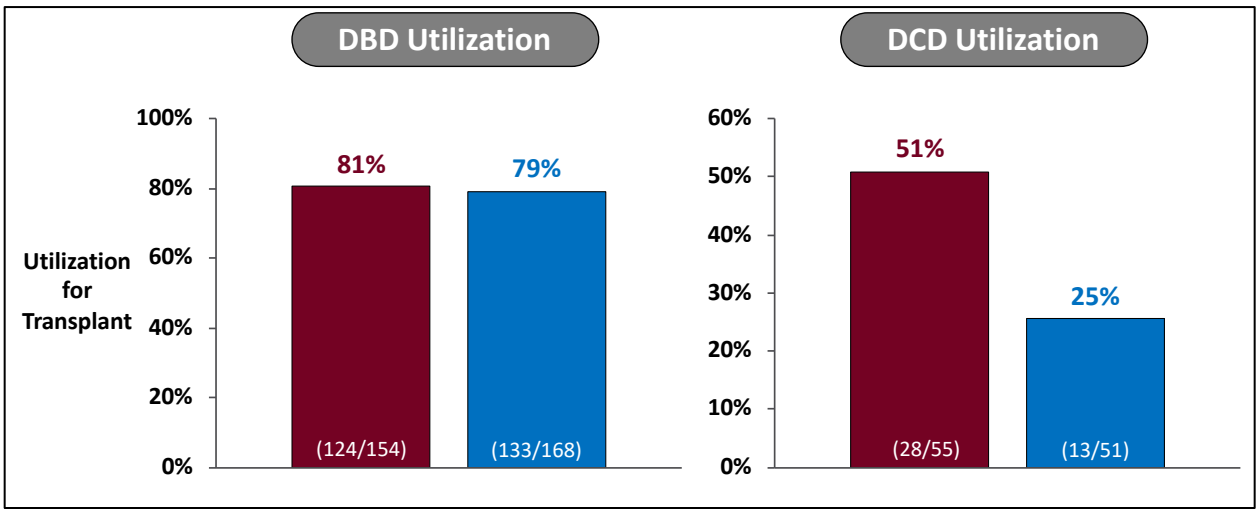
In summary, the unique OCS Liver assessment capability provided a critical opportunity to the transplanting surgeon for additional clinical assessment, which resulted in a clearer understanding of the quality of the donor liver and led to an elimination of donor livers with significant pathology to maximize safety for the transplanted recipients. These results represent a clinical benefit of the OCS Liver System compared to ischemic cold storage which does not enable any assessment of a donor liver allograft once it is removed from the donor body.

Figure 37: Mean OCS Liver Arterial Lactate Trend for Turned Down Donor Livers Compared to OCS Transplanted Donor Livers in PROTECT Trial



Finally, we analyzed the impact of the preservation modality on donor liver utilization for transplantation from DBD and DCD donors in the PROTECT trial. Figure 38 below shows that the use of OCS resulted in a substantially higher rate of utilizing DCD donor livers for transplantation compared to ischemic cold storage (Control). There was no difference in DBD donor liver utilization between the OCS and Control arms.

Figure 38: DBD and DCD Donor Liver Utilization Rates in PROTECT Trial



These data suggest that the OCS Liver System provided an additional opportunity for ex-vivo clinical optimization and assessment of the DCD liver grafts, resulting in doubling the yield of DCD livers transplanted (50.9% vs. 25.5%) compared to the Control arm. These results confirm the potential clinical benefits of machine perfusion to provide additional clinical assessments of the liver allografts. The ability to assess the donor livers allows transplant surgeons to gain more clinical confidence with the liver allograft, and should increase the utilization of donor livers for transplantation and increase access for patients in need in the U.S. DCD livers are seldom transplanted in the U.S. today due to concerns about ischemic/reperfusion injury of the graft and the potential for severe post-transplant ischemic biliary complications (Kwong, et al., 2020, Mateo, et al., 2006; Mathur, et al., 2010).

6.11. Primary Effectiveness Endpoint

The primary effectiveness endpoint, EAD, was adjudicated by the CEC. The OCS Liver PROTECT trial met its primary effectiveness endpoint by demonstrating statistical non-inferiority and superiority of outcomes of the OCS arm compared to Control in both the PP and mITT populations. Specifically, the results demonstrated that use of OCS Liver System was associated with significant reduction of EAD compared to the Control in the primary analysis PP Population (OCS 18.0% vs. Control 31.2%, p=0.0096). The same results were experienced in the mITT population OCS 17.9% vs. 32.4%, p=0.0047. See Figure 39 below.

Figure 39: Primary Effectiveness Endpoint - Incidence of Post-Transplant EAD (PP and mITT Populations)

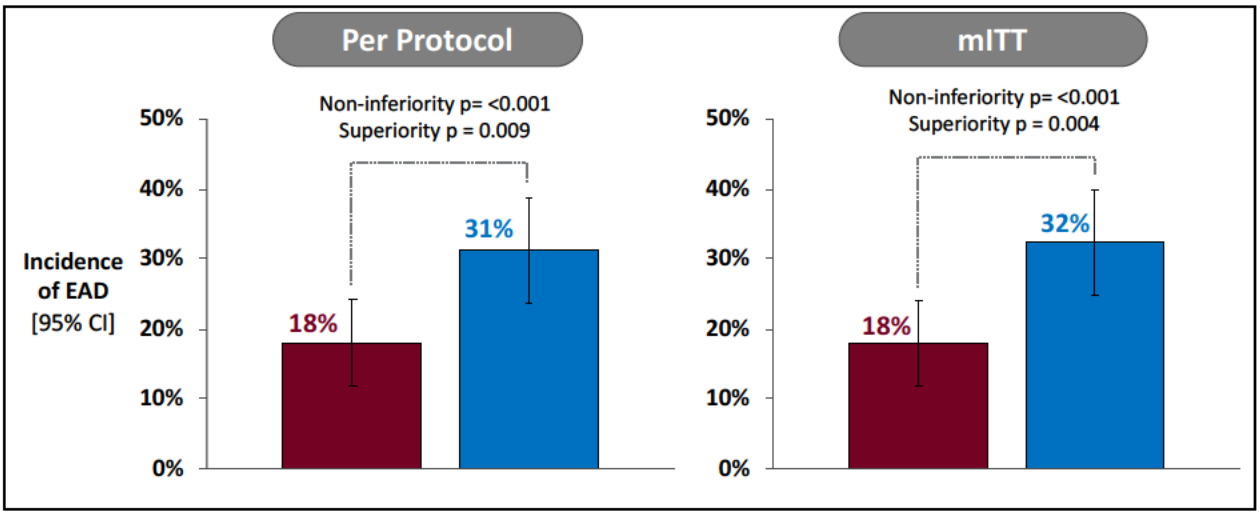


Table 27 below demonstrates the detailed analysis of the primary effectiveness endpoint for the PP population as well as the sensitivity analysis for the mITT population.

Table 27: Primary Effectiveness Endpoint - Incidence of Post-Transplant EAD (PP and mITT Populations)

Variable	Statistics – PP Population	OCS (N=151)	Control (N=142)
Primary effectiveness endpoint: EAD	n/N (%)	27/150 (18.0)	44/141 (31.2)
	95% CI for % (1)	(12.2, 25.1)	(23.7, 39.5)
	Difference in % (OCS - Control)	-0.132	
	95% one-sided upper confidence bound for true difference in proportions (OCS - Control) (2)	-0.049	
	p-value (3)	<0.0001	
	p-value (4)	0.0096	
	Statistics – mITT Population	**OCS (N=152)**	**Control (N=146)**
Primary effectiveness endpoint: EAD	n/N (%)	27/151 (17.9)	47/145 (32.4)
	95% CI for % (1)	(12.1, 24.9)	(24.9, 40.7)
	Difference in % (OCS - Control)	-0.145	
	95% one-sided upper confidence bound for true difference in proportions (OCS - Control) (2)	-0.062	
	p-value (3)	<0.0001	
	p-value (4)	0.0047	

(1) Clopper-Pearson exact confidence interval for a binomial percentage.

(2) 95% one-sided upper confidence bound based on the Farrington and Manning score statistic.

(3) p-value based on the one-sided Farrington and Manning score statistic, testing the null hypothesis that the true OCS proportion is greater than or equal to the true Control proportion + 0.075 vs. the alternative hypothesis that it is less than the true Control proportion plus 0.075.

(4) p-value from a two-sided Fisher's Exact Test, testing the null hypothesis that the true difference in proportions equals 0 vs. the alternative hypothesis that it does not equal 0. This will be done only if the null hypothesis of inferiority is rejected.

In addition, we performed missing data imputation using multiple imputation methods and confirmed the non-inferiority and superiority of OCS vs. Control outcomes. Table 28 below lists the results of the multiple imputation analysis for missing data. We also performed a tipping point analysis, which confirmed that the imputation model is robust with confirmation of results. Table 29 below lists the results of the tipping point analysis. Finally, we performed a pooled site analysis that indicated there is no site effect on the analysis. Table 30 below lists the results of the pooled site analysis. These analyses confirm the robustness of the primary effectiveness endpoint results.

Table 28: Primary Effectiveness Endpoint – Missing Data imputation (PP and mITT Populations)

Variable	Statistics – PP Population	OCS (N=151)	Control (N=142)
Primary effectiveness endpoint: EAD	Estimated Percentage	18.0	31.2
	95% CI for True % (1)	(11.8, 24.1)	(23.5, 38.8)
	Estimated difference in % (OCS - Control)	-0.132	
	95% one-sided upper confidence bound for true difference in proportions (OCS - Control) (2)	-0.048	
	p-value (3)	<0.0001	
	p-value (4)	0.0085	
	Statistics – mITT Population	**OCS (N=152)**	**Control (N=146)**
Primary effectiveness endpoint: EAD	Estimated Percentage	17.9	32.4
	95% CI for True % (1)	(11.8, 24.0)	(24.7, 40.0)
	Estimated difference in % (OCS - Control)	-0.145	
	95% one-sided upper confidence bound for true difference in proportions (OCS - Control) (2)	-0.062	
	p-value (3)	<0.0001	
	p-value (4)	0.0036	

(1) Confidence interval for a binomial percentage based on normal approximation.

(2) 95% one-sided upper confidence bound based on normal approximation.

(3) p-value based on a one-sided normal approximation test, testing the null hypothesis that the true OCS proportion is greater than or equal to the true Control proportion + 0.075 vs. the alternative hypothesis that it is less than the true Control proportion plus 0.075.

(4) p-value from a two-sided normal approximation test, testing the null hypothesis that the true difference in proportions equals 0 vs. the alternative hypothesis that it does not equal 0. This will be done only if the null hypothesis of inferiority is rejected.

Table 29: Tipping Point Analysis (PP and mITT Populations)

Variable	Shift Number [1]	Statistics – PP Population	OCS (N=151)	Control (N=142)
Primary effectiveness endpoint: EAD	0	Estimated Percentage	18.0	31.2
		95% CI for % [2]	(11.8, 24.1)	(23.5, 38.8)
		Estimated Difference in % (OCS - Control)	-0.132	
		95% one-sided upper confidence bound for true difference in proportions (OCS - Control) [3]	-0.048	
		p-value [4]	<0.0001	
		p-value [5]	0.0085	
	1	Estimated Percentage	18.5	31.2
		95% CI for % [2]	(12.3, 24.7)	(23.5, 38.8)
		Estimated Difference in % (OCS - Control)	-0.126	
		95% one-sided upper confidence bound for true difference in proportions (OCS - Control) [3]	-0.043	
		p-value [4]	<0.0001	
		p-value [5]	0.0120	
	Shift Number [1]	**Statistics – mITT Population**	**OCS (N=152)**	**Control (N=146)**
Primary effectiveness endpoint: EAD	0	Estimated Percentage	17.9	32.4
		95% CI for % [2]	(11.8, 24.0)	(24.7, 40.0)
		Estimated Difference in % (OCS - Control)	-0.145	
		95% one-sided upper confidence bound for true difference in proportions (OCS - Control) [3]	-0.062	
		p-value [4]	<0.0001	
		p-value [5]	0.0036	
	1	Estimated Percentage	18.4	32.4
		95% CI for % [2]	(12.3, 24.6)	(24.7, 40.0)
		Estimated Difference in % (OCS - Control)	-0.139	

		95% one-sided upper confidence bound for true difference in proportions (OCS - Control) [3]	-0.056	
		p-value [4]	<0.0001	
		p-value [5]	0.0053	

(1) Shift Number = Number of OCS patients who were shifted to having EAD after imputed as having no EAD.

(2) Confidence interval for a binomial percentage based on normal approximation.

(3) 95% one-sided upper confidence bound based on the normal approximation.

(4) p-value based on a one-sided normal approximation test, testing the null hypothesis that the true OCS proportion is greater than or equal to the true Control proportion + 0.075 vs. the alternative hypothesis that it is less than the true Control proportion plus 0.075.

(5) p-value based on a two-sided normal approximation test, testing the mull hypothesis that the true proportions are equal vs. the alternative hypothesis that they are not equal. This will be done only if the null hypothesis of inferiority is rejected.

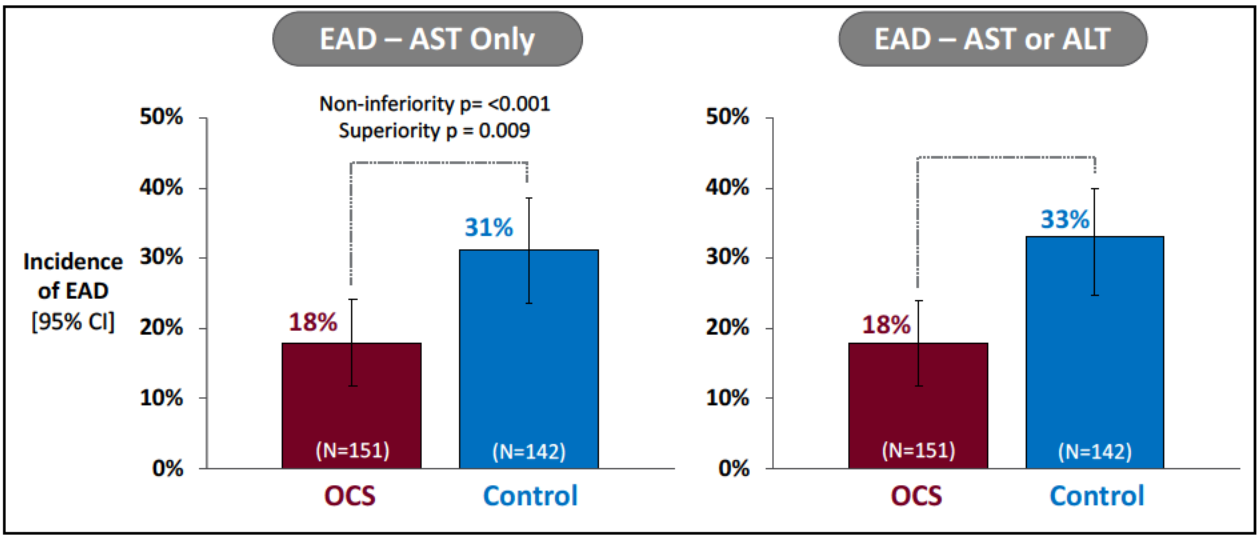
Table 30: Pooled Site Analysis (PP and mITT Populations)

Variable – PP Population	Term in Model	p-value
Primary effectiveness endpoint: EAD	Pooled Site	0.1196
	Pooled Site by treatment interaction	0.1852
Variable – mITT Population	**Term in Model**	**p-value**
Primary effectiveness endpoint: EAD	Pooled Site	0.1277
	Pooled Site by treatment interaction	0.1992

6.11.1. Sensitivity Analysis of Primary Endpoint

FDA has raised a concern about the definition of EAD used in the PROTECT trial, specifically, that it did not include ALT levels. To address FDA's issue, we collected ALT data for the PROTECT trial patients and performed a post-hoc sensitivity analysis of EAD based on both AST and ALT levels and compared it to the pre-specified EAD primary effectiveness endpoint using only AST data. Figure 40 below demonstrates that the addition of ALT levels in the assessment of EAD did not change the overall conclusions and, in fact, resulted in an increased incidence of EAD in the Control arm. This further validates the robustness of using only AST to assess EAD and the robustness of the overall effectiveness endpoint of the PROTECT trial.

Figure 40: Post-hoc Sensitivity Analysis of EAD Based on AST and ALT Levels vs. the Pre-Specified EAD Assessment with AST only in PROTECT Trial (PP Population)



6.12. Secondary Effectiveness Endpoints

The following three secondary effectiveness endpoints were evaluated in the trial and the results of each are described in the sections that follow:

- OCS Measurements during perfusion
- Patient survival at day 30 post-transplantation
- Patient survival at initial hospital discharge post liver transplantation.

6.12.1. OCS Measurement During Perfusion

The advantage of the OCS system is that it allows for continuous monitoring of the donor organ during preservation. The measurements of lactate levels, bile production, hepatic artery pressure, and portal vein pressure were all monitored during the preservation process, as evidenced in Table 31 below.

Table 31: OCS Liver Assessments During Perfusion

Variable	Statistic	OCS (N=155)
OCS Donor Liver Assessment during Perfusion	n/N (proportion)	144/155 (0.93)
	95% one-sided lower confidence bound for proportion [1]	0.885
	p-value [2]	0.0022
Defined as, among donor livers preserved using OCS for the entire preservation period, those livers on which measurements of all of the following during perfusion were available on OCS device before transplant:		
Lactate level (every two hours)	n/N (proportion)	145/155 (0.94)

Variable	Statistic	OCS (N=155)
Average bile production rate (based on total bile production volume and duration of OCS perfusion)	n/N (proportion)	154/155 (0.99)
Hepatic artery pressure (continuously)	n/N (proportion)	155/155 (1.00)
Portal vein pressure (continuously)	n/N (proportion)	155/155 (1.00)

(1) Clopper-Pearson exact confidence bound for a binomial proportion. A lower confidence bound greater than 0.85 results in rejection of the null hypothesis that the true proportion is less than or equal to 0.85 in favor of the alternative hypothesis that the true proportion is greater than 0.85.
(2) p-value from a one-sided exact binomial test, testing the null hypothesis that the true proportion is less than or equal to 0.85 vs. the alternative hypothesis that it is greater than 0.85.

6.12.2. Patient Survival at Day 30 and at Initial Hospital Discharge Post-transplantation

As can be seen in Table 32 and Table 33 below, the OCS arm 30-day survival and survival to initial hospital discharge is non-inferior to the Control arm in both the PP and mITT analysis. Each arm had 1 death within 30 days post-transplant and 2 deaths during the initial hospital admission post-transplant.

Table 32: Patient Survival at Day 30 and at Initial Hospital Discharge (PP Population)

Variable	Statistic	OCS (N=151)	Control (N=142)
1. Patient Survival at Day 30 Post-Transplantation	n/N (%)	150/151 (99.3)	141/142 (99.3)
	95% CI for % [1]	(96.4, 100.0)	(96.1, 100.0)
	Difference in % (Control - OCS)	-0.000	
	95% one-sided upper confidence bound for true difference in proportions (Control - OCS) [2]	0.036	
	p-value [3]	0.0004	
	p-value [4]	1.0000	
2. Patient Survival at Time of Initial Hospital Discharge Post-Transplantation	n/N (%)	149/151 (98.7)	140/142 (98.6)
	95% CI for % [1]	(95.3, 99.8)	(95.0, 99.8)
	Difference in % (Control - OCS)	-0.001	
	95% one-sided upper confidence bound for true difference in proportions (Control - OCS) [2]	0.038	
	p-value [3]	0.0006	
	p-value [4]	1.0000	

(1) Clopper-Pearson exact confidence interval for a binomial percentage.
(2) 95% one-sided upper confidence bound based on the Farrington and Manning score statistic. An upper confidence bound less than 0.075 results in rejection of the null hypothesis of inferiority in favor of the alternative hypothesis of non-inferiority of OCS to Control.

Variable	Statistic	OCS (N=151)	Control (N=142)
(3) p-value based on the one-sided Farrington and Manning score statistic, testing the null hypothesis that the true OCS proportion is less than or equal to the true Control proportion - 0.075 vs. the alternative hypothesis that it is greater than the true Control proportion - 0.075. (4) p-value from a two-sided Fisher's Exact Test, testing the mull hypothesis that the true proportions are equal vs. the alternative hypothesis that they are not equal. This will be done only if the null hypothesis of inferiority is rejected.			

Table 33: Patient Survival at Day 30 and at Initial Hospital Discharge (mITT Population)

Variable	Statistic	OCS (N=152)	Control (N=146)
1. Patient Survival at Day 30 Post-Transplantation	n/N (%)	151/152 (99.3)	145/146 (99.3)
	95% CI for % (1)	(96.4, 100.0)	(96.2, 100.0)
	Difference in % (Control - OCS)	-0.000	
	95% one-sided upper confidence bound for true difference in proportions (Control - OCS) (2)	0.036	
	p-value (3)	0.0004	
	p-value (4)	1.0000	
2. Patient Survival at Time of Initial Hospital Discharge Post-Transplantation	n/N (%)	150/152 (98.7)	144/146 (98.6)
	95% CI for % (1)	(95.3, 99.8)	(95.1, 99.8)
	Difference in % (Control - OCS)	-0.001	
	95% one-sided upper confidence bound for true difference in proportions (Control - OCS) (2)	0.038	
	p-value (3)	0.0006	
	p-value (4)	1.0000	

(1) Clopper-Pearson exact confidence interval for a binomial percentage.
(2) 95% one-sided upper confidence bound based on the Farrington and Manning score statistic. An upper confidence bound less than 0.075 results in rejection of the null hypothesis of inferiority in favor of the alternative hypothesis of non-inferiority of OCS to Control.
(3) p-value based on the one-sided Farrington and Manning score statistic, testing the null hypothesis that the true OCS proportion is less than or equal to the true Control proportion - 0.075 vs. the alternative hypothesis that it is greater than the true Control proportion - 0.075.
(4) p-value from a two-sided Fisher's Exact Test, testing the mull hypothesis that the true proportions are equal vs. the alternative hypothesis that they are not equal. This will be done only if the null hypothesis of inferiority is rejected.

6.13. Other Clinical Endpoints

Other clinical endpoints that were evaluated in the trial and that are presented in this section are:

- Length of initial post-transplant ICU stay

- Length of initial post-transplant hospital stay
- Evidence of ischemic biliary complications diagnosed at 6 months and 12 months
- Extent of reperfusion syndrome as assessed based on the rate of decrease of lactate over the following timepoints: during the anhepatic phase immediately before reperfusion of the transplanted liver; 30-40 minutes after hepatic artery and portal vein reperfusion of the transplanted liver; and 90-120 minutes after reperfusion of the transplanted liver
- Pathology sample score for liver tissue samples taken at the following timepoints: donor liver pre-retrieval; post-OCS and control preservation at the end of back preparation and immediately before the start of re-implantation; and 90-120 minutes after reperfusion of the transplanted liver. All liver biopsies were reviewed in a blinded fashion by the core pathology lab and the methodology for pathology sample score assessment was pre-defined in the PROTECT protocol.

6.13.1. Length of Initial Post-transplant ICU Stay

The ICU stay in hours for the PP population is provided in Table 34. There were no differences noted between the two trial arms.

Table 34: Initial ICU Stay Duration (PP Population)

Variable	Statistic	OCS (N=151)	Control (N=142)
Initial Post-Transplant ICU Stay Duration (hours) [1]	n	150	141
	Mean	107.422	110.576
	Median	60.975	56.200
	SD	201.5703	260.2618
	Minimum - Maximum	10.05 - 1893.47	6.43 - 2669.17
	95% Confidence Interval for Mean [2]	(74.90, 139.94)	(67.24, 153.91)
	Difference in Means (OCS-Control)	-3.15	
	95% Confidence Interval [2]	(-57.12, 50.82)	

(1) Duration based upon clinical order of discharge, where available; otherwise, it is based upon actual discharge date and time.
(2) Confidence interval for the mean or difference in means based on the t-distribution.

6.13.2. Length of Initial Post-transplant Hospital Stay

The length of post-transplant hospital stay in days for the PP population is provided in Table 35 below. There were no differences found between the two trial arms.

Table 35: Hospital Stay Duration (PP Population)

Variable	Statistic	OCS (N=151)	Control (N=142)
Initial Post-Transplant Hospital Stay Duration (days) [1]	n	150	141
	Mean	11.70	11.38
	Median	8.20	8.40
	SD	11.425	12.738
	Minimum - Maximum	2.7 - 78.9	3.3 - 111.2
	95% Confidence Interval for Mean [2]	(9.86, 13.55)	(9.26, 13.50)
	Difference in Means (OCS-Control)	0.32	
	95% Confidence Interval [2]	(-2.47, 3.11)	

(1) Duration based upon clinical order of discharge, where available; otherwise, it is based upon actual discharge date and time.
(2) Confidence interval for the mean or difference in means based on the t-distribution.

6.13.3. Evidence of Ischemic Biliary Complications Diagnosed at 6 and 12 Months Post-transplant

Ischemic biliary complications are one of the most serious complications that negatively impact long-term viability of the liver allograft and the patient. The OCS arm demonstrated a clinically significant difference in the incidence of ischemic biliary complications compared to the Control arm at 6 and 12 months follow-up in both the PP and mITT populations (see Figure 41 and Figure 42 below).

Figure 41: Incidence of Ischemic Biliary Complications from Day of Transplant through 6 Months Follow-up Visit (PP and mITT Populations)

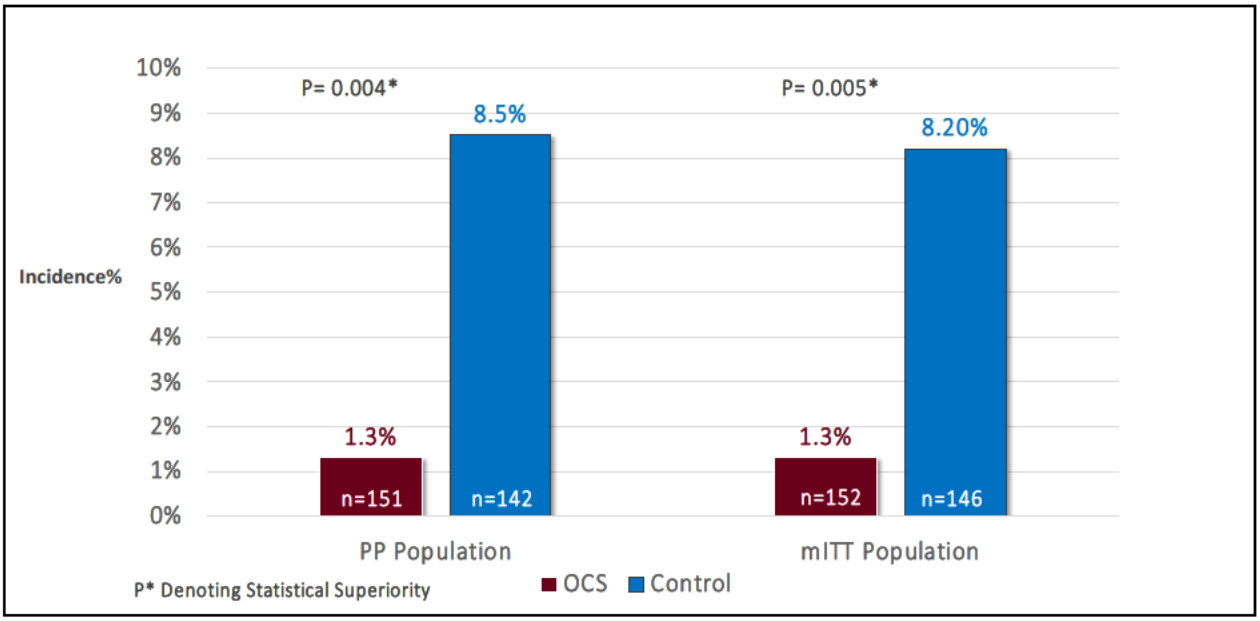
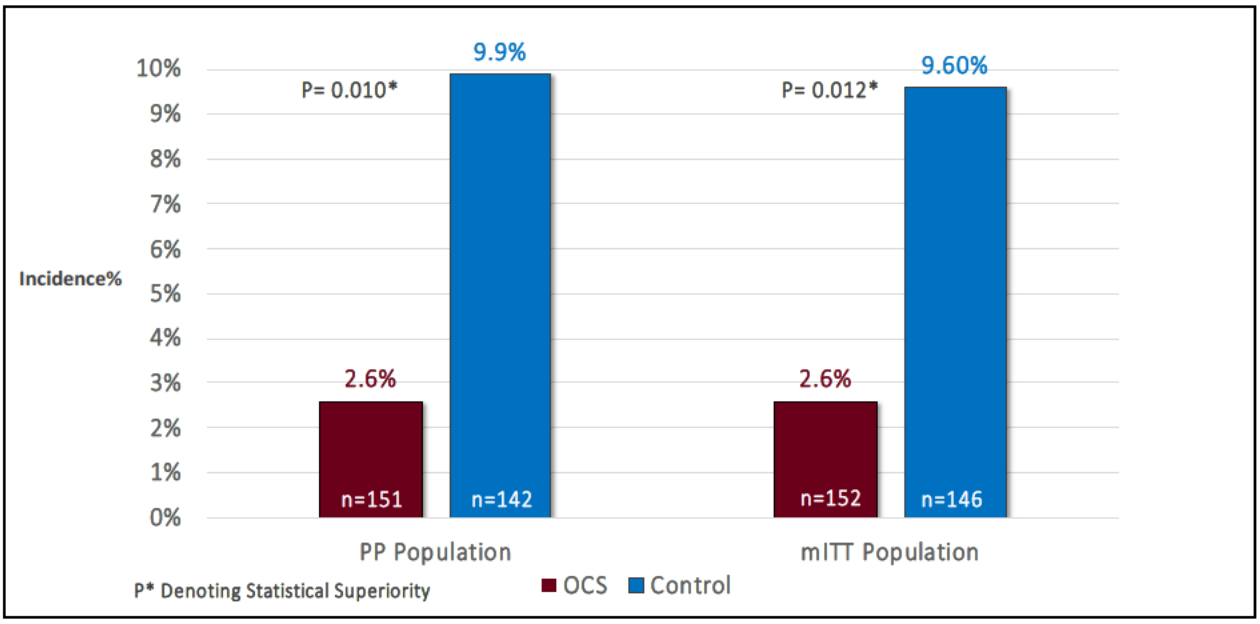


Figure 42: Incidence of Ischemic Biliary Complications from Day of Transplant through 12 Months Follow-up Visit (PP and mITT Populations)



6.13.4. Ad Hoc Analysis of Biliary Complications

At the request of FDA, an additional ad hoc analysis was performed to assess overall biliary complications (both ischemic and non-ischemic) at 30 days post-transplant. Non-ischemic biliary complications are related to surgical technique and are not directly impacted by preservation. The analysis indicated that there is no statistical difference between the OCS and Control in overall biliary complications at 30 days (p=0.3458).

In addition, non-ischemic biliary complications only were analyzed through 30 days post-transplant. No difference was seen between the 2 treatment arms (p=0.1495).

6.13.5. Reperfusion Syndrome

An ad hoc assessment of the extent of reperfusion syndrome was assessed by mean lactate levels post-transplant in the recipient. Reperfusion syndrome was more severe in the Control group compared to OCS based on higher recipient lactate levels post-reperfusion in the donor. (See Table 36 and Table 37 for PP and mITT population, respectively).

Table 36: Assessment of Reperfusion Syndrome – Recipients' Mean Lactate Levels Post-reperfusion in Recipient PP Population)

Timepoint	OCS Recipient arterial lactate (mmol/L) N=151 Mean ± SD	Control Recipient arterial lactate (mmol/L) N=142 Mean ± SD
Anhepatic	3.47 ± 1.712	3.49 ± 1.455
0-40 min after reperfusion	4.03 ± 2.088	4.48 ± 2.379
90-120/150 min after reperfusion	3.62 ± 2.219	4.25 ± 2.89

Table 37: Assessment of Reperfusion Syndrome – Recipients' Lactate Levels Post-reperfusion in Recipient (mITT Population)

Timepoint	OCS Recipient Arterial Lactate (mmol/L) ± SD) N=152	Control Recipient Arterial Lactate (mmol/L) ± SD) N=146
Anhepatic	3.47 ± 1.706	3.55 ± 1.621
0-40 min after reperfusion	4.05 ± 2.092	4.57 ± 2.532
90-120/150 min after reperfusion	3.64 ± 2.220	4.33 ± 2.987

In addition, reperfusion syndrome was assessed between the OCS and Control based on the increase in lactate from anhepatic phase through 90-120/150 minutes after reperfusion. The incidence of reperfusion syndrome was numerically lower in the OCS group as outlined in Table 38 below.

Additional ad hoc analyses were performed to examine reperfusion syndrome by stratifying all trial recipients by presence or absence of EAD. As can be seen in Table 39, there is a significant association between EAD and reperfusion syndrome as well as with EAD and a greater slope of the lactate change in both the mITT and PP populations.

Table 38: Reperfusion Syndrome as Defined by Increase in Lactate: Results (AT and PP Populations)

Variable	Statistics – AT Population	OCS (N=153)	Control (N=146)
Reperfusion Syndrome[2]	n/N	67/146	75/136
	Prevalence	0.459	0.551
	95% Confidence Interval for Difference in Prevalences (OCS - Control)	(-0.209, 0.024)	
Variable	**Statistics – PP Population**	**OCS (N=151)**	**Control (N=142)**

Variable	Statistics – AT Population	OCS (N=153)	Control (N=146)
Reperfusion Syndrome[2]	n/N	66/144	72/132
	Prevalence	0.458	0.545
	95% Confidence Interval for Difference in Prevalences (OCS - Control)	(-0.205, 0.031)	

(1) p-value from chi-square test, testing the null hypothesis that the prevalences are equal for the two treatments vs. the alternative hypothesis that they are not equal.
(2) Reperfusion syndrome was defined as an increase in lactate from anhepatic phase through 90-120/150 minutes post reperfusion

Table 39: Reperfusion Syndrome as Defined by Increase in Lactate and Over Time (EAD vs No EAD) (mITT and PP Populations)

Variable	Statistics – mITT Population	EAD (N=74)	No EAD (N=222)
Reperfusion Syndrome[4]	Yes	45 (65.2)	96 (45.5)
	No	24 (34.8)	115 (54.5)
	p-value [(1)]	0.0054	
Lactate change over time (slope) from anhepatic phase through ~120 minutes post-reperfusion	n/N	69/74	211/222
	Mean	0.665	0.139
	Median	0.250	-0.050
	SD	1.3647	0.9704
	Minimum - Maximum	-1.15 – 7.13	-2.45 – 6.65
	95% Confidence Interval for Mean [(2)]	(0.337, 0.993)	(0.007, 0.271)
	Difference in Means (EAD-NO EAD)	0.526	
	95% Confidence Interval for Differences in Means [(2)]	(0.173, 0.878)	
	p-value [(3)]	0.0039	
Variable	**Statistics – PP Population**	**EAD (N=71)**	**No EAD (N=220)**
Reperfusion Syndrome[4]	Yes	43 (65.2)	94 (45.0)
	No	23 (34.8)	115 (55.0)
	p-value [(1)]	0.0048	
Lactate change over time (slope) from anhepatic phase through ~120 minutes post-reperfusion	n/N	66/71	209/220
	Mean	0.678	0.132
	Median	0.275	-0.050
	SD	1.3901	0.9719
	Minimum - Maximum	-1.15 – 7.13	-2.45 – 6.65

	95% Confidence Interval for Mean [2]	(0.337, 1.020)	(0.001, 0.264)
	Difference in Means (EAD-NO EAD)	0.547	
	95% Confidence Interval for Differences in Means [2]	(0.181, 0.912)	
	p-value [3]	0.0038	

(1) p-value from Fisher's Exact Test
(2) Confidence interval for the mean or difference in means based on the t-distribution.
(3) p-value from a two-sided, two-sample t-test, testing the null hypothesis that the means are equal for the two treatments vs. the alternative hypothesis that they are not equal.
(4) Reperfusion syndrome was defined as an increase in lactate from anhepatic phase through 90-120/150 minutes post reperfusion

6.13.6. Liver Pathology Assessment and Scoring

Biopsy specimens were provided to the central core for processing after collection at three timepoints during the liver retrieval and transplantation process: at the time of donor liver pre-retrieval, post-OCS and Control preservation prior to transplantation and 90-120 minutes post-reperfusion of the transplanted liver in the recipient abdomen.

High-resolution (x40) whole-slide images of formalin-fixed, paraffin embedded, H&E stained 4-µm tissue sections of liver biopsy samples were scored for histopathologic criteria by a central pathologist without knowledge of any clinical data, serologic data, or experimental treatment other than the date of transplantation and original disease. Specimen comparison across timepoints was then evaluated for progression of noted pathology. Scoring metrics were based on an amalgamation of criteria for assessing reperfusion injury, including: necrosis, inflammation (including distribution and type of inflammatory cells), steatosis (Kakizoe, et al., 1990; Abraham, et al., 1996; Gaffey, et al., 1997; Ali, et al., 2015; Spetzler, et al., 2015). A protocolized scoring template was developed by the core pathologist for inclusion in the lab's Digital Telepathology software system. Extra-Hepatic Bile Duct changes were also evaluated at a single timepoint (Hansen, et al., 2012) for bleeding, lesions, arteriolonecrosis, duct necrosis, inflammation, and gland injury.

For turned down livers, the entire liver was sent to the central lab for grossing by the central pathologist. Evaluation included an anatomical evaluation as well as specimen sampling throughout multiple lobes. Scoring of the liver followed the same template as the biopsies with inclusion of diagnostic notes related to suggested cause of organ turndown.

The overall pathology score which included assessments at all three timepoints showed no differences between the OCS and Control tissue sample scores as outlined in Table 40 below. However, differences were noted in the incidence of lobular inflammation post-transplant in biopsies obtained at 90-120 minutes post-reperfusion, which was scored as normal-minimal, mild, and moderate-severe by the independent core pathologist. Lobular inflammation is an established marker of ischemia reperfusion injury (Ali, et al., 2015; Kakizoe, et al., 1990; Sosa, et al., 2016).

Table 40: Results of the Average Pathology Sample Scores for the Three Samples Timepoints (AT and PP Populations)

Variable	Statistics – AT Population	OCS (N=153)	Control (N=146)
Average Overall Pathology Sample Score	n	151	139
	Mean	0.997	1.068
	Median	1.000	1.000
	SD	0.8021	0.8340
	Minimum - Maximum	0.25 - 3.00	0.00 - 3.00
	95% Confidence Interval for Mean (1)	(0.87, 1.13)	(0.93, 1.21)
	Difference in Means (OCS-Control)	-0.07	
	95% Confidence Interval (1)	(-0.26, 0.12)	
Variable	**Statistics – PP Population**	**OCS (N=151)**	**Control (N=142)**
Average Overall Pathology Sample Score	n	149	135
	Mean	1.005	1.061
	Median	1.000	1.000
	SD	0.8041	0.8289
	Minimum - Maximum	0.25 - 3.00	0.00 - 3.00
	95% Confidence Interval for Mean (1)	(0.87, 1.14)	(0.92, 1.20)
	Difference in Means (OCS-Control)	-0.06	
	95% Confidence Interval (1)	(-0.25, 0.13)	

(1) Confidence interval for the mean or difference in means based on the t-distribution.
(2) p-value from a two-sided, two-sample t-test, testing the null hypothesis that the means are equal for the two treatments vs. the alternative hypothesis that they are not equal.

Additional *ad hoc* analyses were performed to further examine overall pathology score by stratifying recipients in both groups by DCD and DBD organs in Table 41 below. The results show a substantial decrease in pathology score for DCD organs in the OCS arm compared to the Control.

Table 42 below stratifies the overall pathology score for the overall patient population by the presence or absence of EAD. There is a significant association between higher mean pathology scores and EAD in both the mITT and PP populations.

Table 41: Pathology Score for DCD and DBD (PP Population)

Variable	Statistics	DCD OCS (N-151)	DCD Control (N=142)	DBD OCS (N-151)	DBD Control (N=142)
Average Overall Pathology Sample Score	n/N	27/151	11/142	122/151	124/142
	Mean	1.194	2.000	0.963	0.978
	Median	1.000	2.000	1.000	1.000
	SD	0.9616	0.8062	0.7631	0.7809
	Minimum - Maximum	0.25-3.00	1.00-3.00	0.25-3.00	0.00-3.00
	95% Confidence Interval for Mean (1)	(0.814, 1.575)	(1.458, 2.542)	(0.826, 1.100)	(0.839, 1.117)
	Difference in Means (OCS-Control)	-0.81		-0.01	
	95% Confidence Interval for Differences in Means (1)	(-1.47, -0.14)		(-0.21, 0.18)	

(1) Confidence interval for the mean or difference in means based on the t-distribution.

Table 42: Pathology Score by EAD vs No EAD (mITT and PP Populations)

Variable	Statistics – mITT Population	EAD (N=74)	No EAD (N=222)
Average Overall Pathology Sample Score	n/N	73/74	216/222
	Mean	1.312	0.939
	Median	1.000	0.750
	SD	0.8618	0.7821
	Minimum - Maximum	0.00 – 3.00	0.25 – 3.00
	95% Confidence Interval for Mean (1)	(1.111, 1.513)	(0.834, 1.044)
	Difference in Means (EAD-NO EAD)	0.373	
	95% Confidence Interval for Differences in Means (1)	(0.159, 0.587)	
	p-value (2)	0.0007	
Variable	**Statistics – PP Population**	**EAD (N=71)**	**No EAD (N=220)**
Average Overall Pathology Sample Score	n/N	70/71	214/220
	Mean	1.329	0.935
	Median	1.000	0.750

	SD	0.8614	0.7770
	Minimum - Maximum	0.00 – 3.00	0.25 – 3.00
	95% Confidence Interval for Mean [1]	(1.123, 1.534)	(0.830, 1.039)
	Difference in Means (EAD-NO EAD)	0.394	
	95% Confidence Interval for Differences in Means [1]	(0.178, 0.610)	
	p-value [2]	0.0004	

(1) Confidence interval for the mean or difference in means based on the t-distribution.
(2) p-value from a two-sided, two-sample t-test, testing the null hypothesis that the means are equal for the two treatments vs. the alternative hypothesis that they are not equal.

6.14. Kaplan-Meier Recipient and Graft Survival

At the time of the data cut-off, all PROTECT patients have had their 12-month follow-up visit and 123 of 300 (41%) patients have had their 24-month visit. There are no statistically significant differences seen in patient or graft survival between the OCS and Control groups for both the PP and mITT populations.

Kaplan-Meier patient survival curves are shown in Figure 43 for the PP population and in Figure 44 for the mITT population. Note that Control Patient (b)(6) died on Day 0 in the operating room prior to transplant and is not included in the Kaplan-Meier estimates.

Figure 43: Kaplan-Meier Recipient Survival (PP Population)

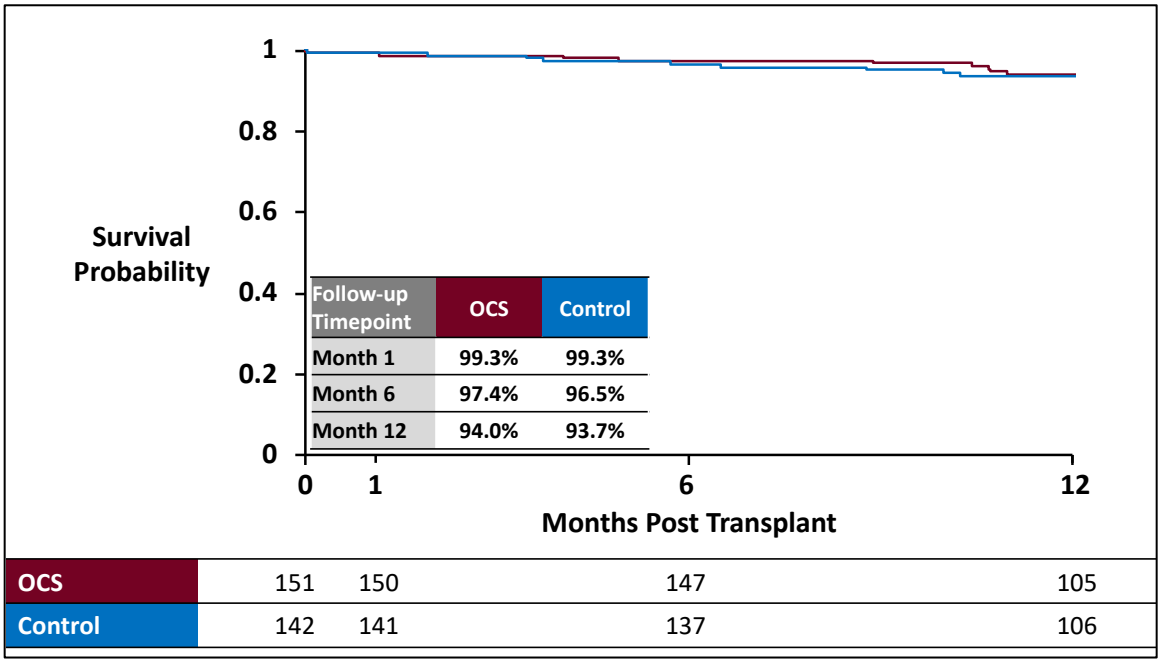
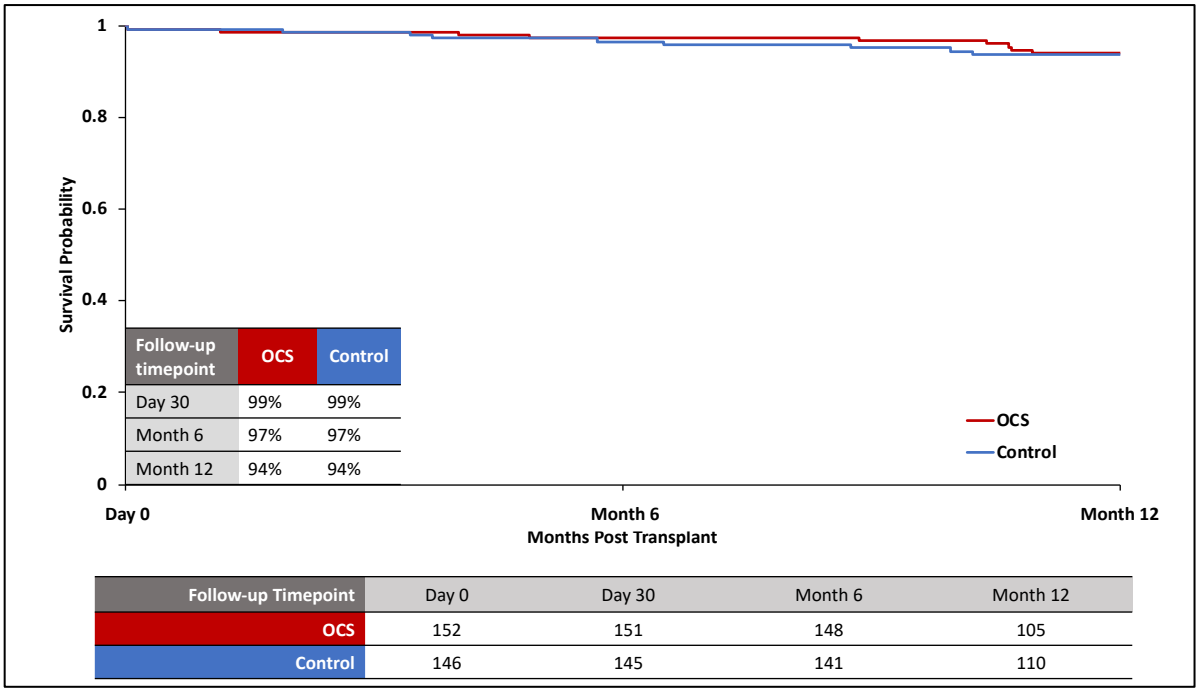


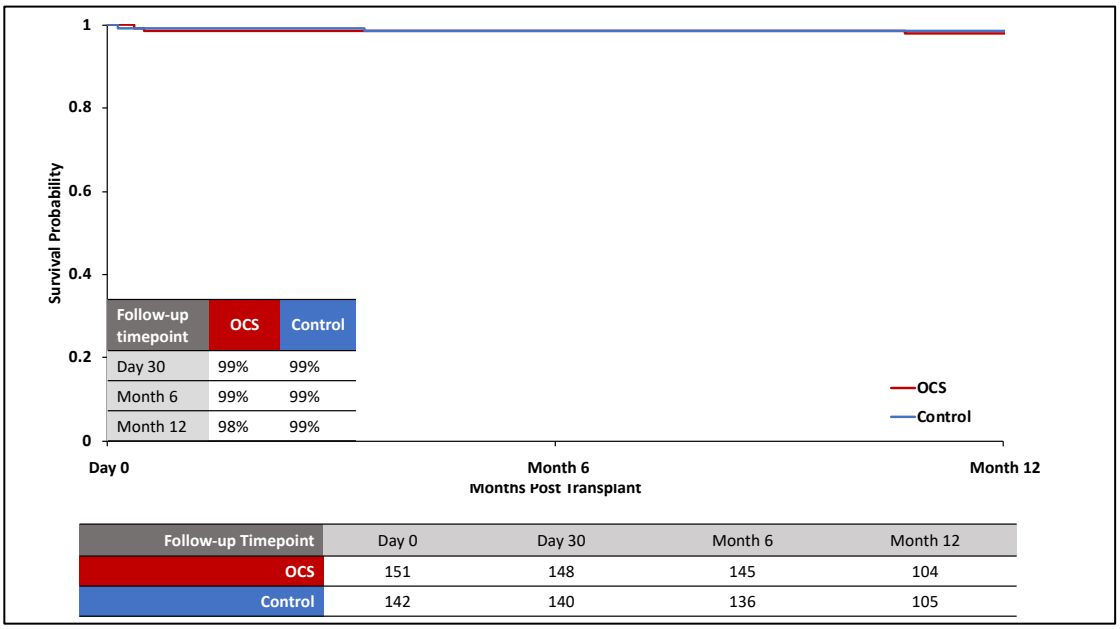
Figure 44: Kaplan-Meier Recipient Survival (mITT Population)



Follow-up Timepoint	Day 0	Day 30	Month 6	Month 12
OCS	152	151	148	105
Control	146	145	141	110

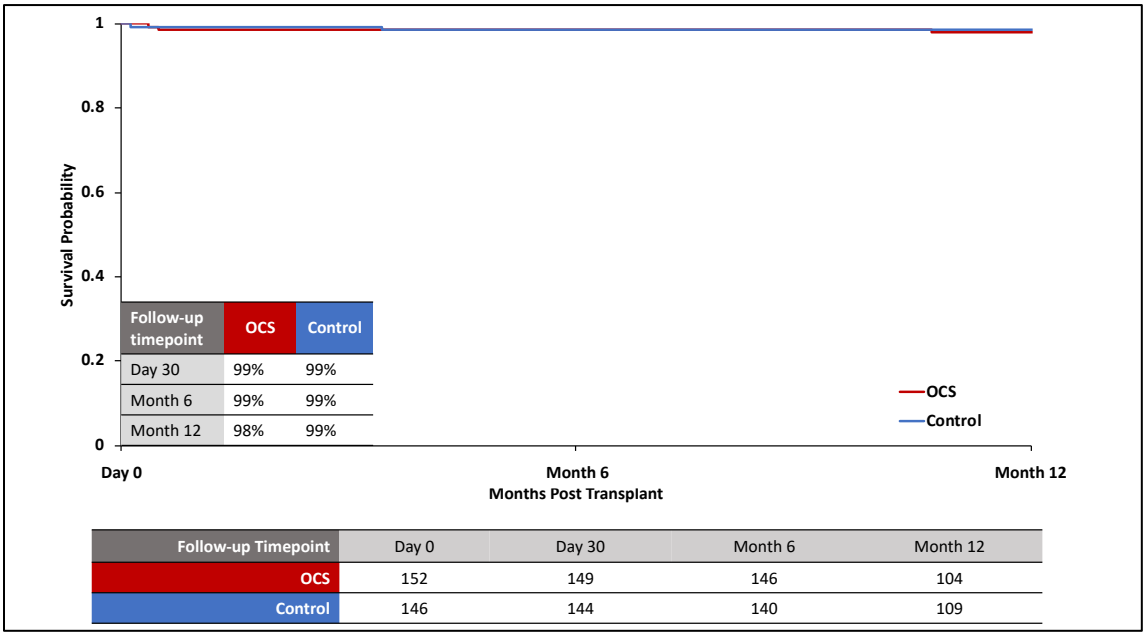
Kaplan Meier graft survival is shown in Figure 45 for the PP population and Figure 46 for the mITT population. Through 12 months post-transplant in both the PP and mITT populations, there were 3 patients re-transplanted (Patients (b)(6) (OCS), (b)(6) (OCS), and (b)(6) (Control)) and 2 patients whose cause of death was adjudicated as liver graft-related (Patients (b)(6) (Control) and (b)(6) (OCS)).

Figure 45: Kaplan-Meier Liver Graft Survival (PP Population)



Follow-up Timepoint	Day 0	Day 30	Month 6	Month 12
OCS	151	148	145	104
Control	142	140	136	105

Figure 46: Kaplan-Meier Liver Graft Survival (mITT Population)



Follow-up Timepoint	Day 0	Day 30	Month 6	Month 12
OCS	152	149	146	104
Control	146	144	140	109

6.15. Recipient Cause of Death Summary

A total of 22 patients died in the OCS Liver PROTECT trial, 11 in the OCS Arm and 11 in the Control arm. The CEC-adjudicated causes of death are listed in Appendix 3.

6.16. Safety Endpoint

The safety endpoint for the trial was defined as the average number of LGRSAEs up to the 30-day follow-up after transplantation, consisting of the following serious adverse events:

- Primary non-function (defined as irreversible graft dysfunction requiring emergency liver re-transplantation or death with the first 10 days, in the absence of immunologic or surgical causes)
- Ischemic biliary complications (ischemic biliary strictures, and non-anastomotic bile duct leaks)
- Vascular complications (liver graft-related coagulopathy, hepatic artery stenosis, hepatic artery thrombosis, and portal vein thrombosis)
- Liver allograft infections (liver abscess, cholangitis, etc.).

As can be seen in Table 43 below, LGRSAEs with the OCS within the first 30 days post-transplantation demonstrated non-inferiority to the Control group.

Table 43: Number of LGRSAEs During the First 30 Days Post-transplantation (AT Population)

Variable	Statistic	OCS (N=153)	Control (N=146)	Difference in Means (OCS - Control) (95% CI) [1]
Number of LGRSAEs up to the 30-day follow-up after transplantation per patient (at most one per type per patient)	n	153	146	
	Mean	0.046	0.075	-0.030 (-0.084, 0.025)
	Median	0.0	0.0	
	SD	0.2096	0.2649	
	Minimum - Maximum	0 - 1	0 - 1	
	95% CI for Mean [1]	(0.012, 0.079)	(0.032, 0.119)	
	p-value [2]			<0.0001
	p-value [3]			0.2865

(1) Confidence interval based on the t-distribution.
(2) p-value from a one-sided two-sample t-test, testing the null hypothesis that the true OCS mean is greater than or equal to the Control mean plus the non-inferiority margin of 1.0 vs. the alternative hypothesis that it is less than the Control mean plus 1.0.
(3) p-value from a two-sided, two-sample t-test, testing the null hypothesis that the means are equal for the two treatments vs. the alternative hypothesis that they are not equal. This test will only be performed if non-inferiority is demonstrated.

The type of LGRSAEs within 30 days are provided in Table 44 below. As can be noted, there are no ischemic biliary complications in the OCS arm and the vascular complications are reduced in the OCS arm vs. the Control.

Table 44: LGRSAEs within 30 Days (AT Population)

Variable	OCS (N=153)		Control (N=146)	
	Patients n (%)	Events n (%)	Patients n (%)	Events n (%)
Patients with at least one LGRSAE within 30 days post-transplant	7 (4.6%)	8	11 (7.5%)	13
Non-functioning graft	0	0	0	0
Ischemic biliary complications	0	0	2 (1.4%)	2 (15.4%)
Vascular complications	7 (4.6%)	8 (100%)	9 (6.2%)	11 (84.6%)
Liver allograft infections	0	0	0	0

6.16.1. LGRSAEs within 6 Months

A pre-specified analysis of LGRSAEs within 180 days (6 months) post-transplant is provided in Table 45. A trend in reduction of the ischemic biliary complications and vascular complications in the OCS arm vs. the Control can be seen.

Table 45: LGRSAEs within 6 Months Post-transplant (AT Population)

Variable	OCS (N=153)		Control (N=146)	
	Patients n (%)	Events n (%)	Patients n (%)	Events n (%)
Patients with at least one LGRSAE 6 months post-transplant	9 (5.9%)	10	23 (15.8%)	28
Non-functioning graft	0	0	0	0
Ischemic biliary complications	2 (1.3%)	2 (20.0%)	12 (8.2%)	12 (42.9%)
Vascular complications	7 (4.6%)	8 (80.0%)	12 (8.2%)	15 (53.6%)
Liver allograft infections	0	0	1 (0.7%)	1 (3.6%)

6.17. Overall Serious Adverse Events (SAEs)

SAEs were collected through 30 days post-transplant or initial hospital discharge. LGRSAEs were collected through 6 months post-transplant, and ischemic biliary complications were collected through 12 months post-transplant. A comprehensive summary of all of these events is shown in Table 46 below. As previously discussed, ischemic biliary complications were lower in the OCS group compared to the Control group. The remaining SAEs were typical of those experienced by liver transplant patients, and there were no differences between the two groups in the overall number of adverse events.

Table 46: CEC-adjudicated Treatment-Emergent SAEs by System Organ Class and Preferred Term (AT Population) - Comprehensive Listing Includes all SAEs through 30 days/hospital discharge post-transplant and LGRSAEs through 6 months and ischemic biliary complications through 12 months post-transplant

System Organ Class/Preferred Term	OCS (N=153)		Control (N=146)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
Any serious adverse event	82 (53.6)	150	72 (49.3)	148
Blood and lymphatic system disorders	4 (2.6)	4 (2.7)	2 (1.4)	2 (1.4)
• Anaemia	3 (2.0)	3 (2.0)	1 (0.7)	1 (0.7)
• Febrile neutropenia	1 (0.7)	1 (0.7)	0	0
• Intravascular haemolysis	0	0	1 (0.7)	1 (0.7)
Cardiac disorders	7 (4.6)	9 (6.0)	9 (6.2)	11 (7.4)
• Angina pectoris	0	0	1 (0.7)	1 (0.7)
• Arrhythmia	0	0	2 (1.4)	2 (1.4)
• Atrial fibrillation	3 (2.0)	3 (2.0)	4 (2.7)	4 (2.7)
• Atrioventricular block second degree	1 (0.7)	1 (0.7)	0	0
• Cardiac arrest	1 (0.7)	1 (0.7)	0	0

System Organ Class/Preferred Term	OCS (N=153)		Control (N=146)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
• Intracardiac thrombus	2 (1.3)	2 (1.3)	2 (1.4)	3 (2.0)
• Myocardial ischaemia	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)
• Tachycardia	1 (0.7)	1 (0.7)	0	0
Gastrointestinal disorders	15 (9.8)	16 (10.7)	9 (6.2)	9 (6.1)
• Abdominal pain	2 (1.3)	2 (1.3)	0	0
• Abdominal pain upper	1 (0.7)	1 (0.7)	0	0
• Ascites	1 (0.7)	1 (0.7)	3 (2.1)	3 (2.0)
• Coeliac artery compression syndrome	1 (0.7)	1 (0.7)	0	0
• Diarrhoea	1 (0.7)	1 (0.7)	0	0
• Duodenal perforation	1 (0.7)	1 (0.7)	0	0
• Gastrointestinal haemorrhage	0	0	2 (1.4)	2 (1.4)
• Haematemesis	1 (0.7)	1 (0.7)	0	0
• Haematochezia	0	0	1 (0.7)	1 (0.7)
• Haemorrhoids	1 (0.7)	1 (0.7)	0	0
• Ileus	1 (0.7)	1 (0.7)	0	0
• Intestinal haemorrhage	0	0	1 (0.7)	1 (0.7)
• Nausea	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)
• Pancreatitis	0	0	1 (0.7)	1 (0.7)
• Peritonitis	2 (1.3)	2 (1.3)	0	0
• Pneumoperitoneum	1 (0.7)	1 (0.7)	0	0
• Small intestinal obstruction	1 (0.7)	1 (0.7)	0	0
• Umbilical hernia	1 (0.7)	1 (0.7)	0	0
General disorders and administration site conditions	3 (2.0)	3 (2.0)	5 (3.4)	6 (4.1)
• Catheter site haemorrhage	0	0	1 (0.7)	1 (0.7)
• Oedema	1 (0.7)	1 (0.7)	0	0
• Oedema peripheral	0	0	1 (0.7)	1 (0.7)
• Pyrexia	2 (1.3)	2 (1.3)	4 (2.7)	4 (2.7)
Hepatobiliary disorders	12 (7.8)	13 (8.7)	22 (15.1)	24 (16.2)
• Bile duct obstruction	1 (0.7)	1 (0.7)	0	0
• Bile duct stenosis	1 (0.7)	1 (0.7)	0	0

System Organ Class/Preferred Term	OCS (N=153)		Control (N=146)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
• Biliary ischaemia	4 (2.6)	4 (2.7)	14 (9.6)	14 (9.5)
• Cholangitis	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)
• Hepatic artery stenosis	2 (1.3)	2 (1.3)	4 (2.7)	4 (2.7)
• Hepatic artery thrombosis	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)
• Hepatic necrosis	1 (0.7)	1 (0.7)	0	0
• Portal vein occlusion	0	0	1 (0.7)	1 (0.7)
• Portal vein stenosis	0	0	1 (0.7)	1 (0.7)
• Portal vein thrombosis	2 (1.3)	2 (1.3)	2 (1.4)	2 (1.4)
Immune system disorders	6 (3.9)	6 (4.0)	7 (4.8)	8 (5.4)
• Hypersensitivity	1 (0.7)	1 (0.7)	0	0
• Transplant rejection	5 (3.3)	5 (3.3)	7 (4.8)	8 (5.4)
Infections and infestations	13 (8.5)	13 (8.7)	4 (2.7)	4 (2.7)
• Bacteraemia	2 (1.3)	2 (1.3)	1 (0.7)	1 (0.7)
• Cellulitis	1 (0.7)	1 (0.7)	0	0
• Fungal peritonitis	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)
• Influenza	1 (0.7)	1 (0.7)	0	0
• Pneumonia	2 (1.3)	2 (1.3)	0	0
• Sepsis	2 (1.3)	2 (1.3)	1 (0.7)	1 (0.7)
• Septic shock	0	0	1 (0.7)	1 (0.7)
• Urinary tract infection	1 (0.7)	1 (0.7)	0	0
• Wound infection	3 (2.0)	3 (2.0)	0	0
Injury, poisoning and procedural complications	27 (17.6)	35 (23.3)	29 (19.9)	33 (22.3)
• Anastomotic haemorrhage	1 (0.7)	1 (0.7)	0	0
• Biliary anastomosis complication	13 (8.5)	13 (8.7)	6 (4.1)	6 (4.1)
• Drug toxicity	5 (3.3)	5 (3.3)	2 (1.4)	2 (1.4)
• Gastrointestinal anastomotic leak	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)
• Mental status changes postoperative	1 (0.7)	1 (0.7)	2 (1.4)	2 (1.4)
• Operative haemorrhage	0	0	1 (0.7)	1 (0.7)
• Post procedural bile leak	4 (2.6)	4 (2.7)	11 (7.5)	11 (7.4)
• Post procedural haemorrhage	5 (3.3)	5 (3.3)	7 (4.8)	7 (4.7)

System Organ Class/Preferred Term	OCS (N=153)		Control (N=146)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
• Procedural complication	0	0	2 (1.4)	2 (1.4)
• Seroma	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)
• Spinal fracture	1 (0.7)	1 (0.7)	0	0
• Vascular procedure complication	1 (0.7)	1 (0.7)	0	0
• Wound dehiscence	2 (1.3)	2 (1.3)	0	0
Investigations	2 (1.3)	2 (1.3)	1 (0.7)	1 (0.7)
• Liver function test abnormal	2 (1.3)	2 (1.3)	1 (0.7)	1 (0.7)
Metabolism and nutrition disorders	7 (4.6)	7 (4.7)	1 (0.7)	1 (0.7)
• Failure to thrive	2 (1.3)	2 (1.3)	1 (0.7)	1 (0.7)
• Fluid overload	1 (0.7)	1 (0.7)	0	0
• Hyperkalaemia	2 (1.3)	2 (1.3)	0	0
• Hyponatraemia	1 (0.7)	1 (0.7)	0	0
• Malnutrition	1 (0.7)	1 (0.7)	0	0
Musculoskeletal and connective tissue disorders	0	0	1 (0.7)	1 (0.7)
• Rhabdomyolysis	0	0	1 (0.7)	1 (0.7)
Nervous system disorders	4 (2.6)	6 (4.0)	10 (6.8)	14 (9.5)
• Cerebral haemorrhage	0	0	2 (1.4)	2 (1.4)
• Cerebrovascular accident	0	0	1 (0.7)	2 (1.4)
• Convulsion	2 (1.3)	2 (1.3)	5 (3.4)	5 (3.4)
• Demyelinating polyneuropathy	1 (0.7)	1 (0.7)	0	0
• Encephalopathy	1 (0.7)	1 (0.7)	0	0
• Headache	1 (0.7)	1 (0.7)	0	0
• Hemiparesis	1 (0.7)	1 (0.7)	0	0
• Hepatic encephalopathy	0	0	1 (0.7)	1 (0.7)
• Ischaemic stroke	0	0	1 (0.7)	1 (0.7)
• Metabolic encephalopathy	0	0	1 (0.7)	1 (0.7)
• Migraine	0	0	1 (0.7)	1 (0.7)
• Subarachnoid haemorrhage	0	0	1 (0.7)	1 (0.7)
Psychiatric disorders	2 (1.3)	2 (1.3)	4 (2.7)	4 (2.7)
• Delirium	1 (0.7)	1 (0.7)	4 (2.7)	4 (2.7)

System Organ Class/Preferred Term	OCS (N=153)		Control (N=146)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
• Mental status changes	1 (0.7)	1 (0.7)	0	0
Renal and urinary disorders	13 (8.5)	13 (8.7)	8 (5.5)	8 (5.4)
• Renal failure	2 (1.3)	2 (1.3)	1 (0.7)	1 (0.7)
• Renal failure acute	11 (7.2)	11 (7.3)	7 (4.8)	7 (4.7)
Respiratory, thoracic, and mediastinal disorders	10 (6.5)	11 (7.3)	13 (8.9)	15 (10.1)
• Acute respiratory distress syndrome	1 (0.7)	1 (0.7)	0	0
• Acute respiratory failure	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)
• Bronchial secretion retention	0	0	1 (0.7)	1 (0.7)
• Haemothorax	0	0	2 (1.4)	2 (1.4)
• Hypoxia	0	0	1 (0.7)	1 (0.7)
• Pleural effusion	1 (0.7)	1 (0.7)	4 (2.7)	4 (2.7)
• Pneumothorax	1 (0.7)	1 (0.7)	0	0
• Pulmonary embolism	2 (1.3)	2 (1.3)	0	0
• Pulmonary hypertension	1 (0.7)	1 (0.7)	2 (1.4)	2 (1.4)
• Pulmonary oedema	1 (0.7)	1 (0.7)	0	0
• Reexpansion pulmonary oedema	0	0	1 (0.7)	1 (0.7)
• Respiratory failure	3 (2.0)	3 (2.0)	3 (2.1)	3 (2.0)
Surgical and medical procedures	2 (1.3)	3 (2.0)	0	0
• Hernia repair	1 (0.7)	1 (0.7)	0	0
• Incisional drainage	1 (0.7)	1 (0.7)	0	0
• Inguinal hernia repair	1 (0.7)	1 (0.7)	0	0
Vascular disorders	7 (4.6)	7 (4.7)	7 (4.8)	7 (4.7)
• Air embolism	0	0	1 (0.7)	1 (0.7)
• Artery dissection	1 (0.7)	1 (0.7)	0	0
• Deep vein thrombosis	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)
• Haematoma	1 (0.7)	1 (0.7)	0	0
• Haemorrhage	1 (0.7)	1 (0.7)	2 (1.4)	2 (1.4)
• Hypovolaemic shock	1 (0.7)	1 (0.7)	0	0
• Jugular vein thrombosis	1 (0.7)	1 (0.7)	0	0
• Reperfusion injury	0	0	1 (0.7)	1 (0.7)

System Organ Class/Preferred Term	OCS (N=153)		Control (N=146)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
• Shock	0	0	1 (0.7)	1 (0.7)
• Vascular shunt	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)

6.18. Device Malfunctions

There were 3/155 (1.9%) reported OCS device malfunctions in the OCS Liver PROTECT trial. No malfunctions led to loss of an organ or recipient risk/harm.

- Two of 3 malfunctions (Patients (b)(6) and (b)(6)) were of small plastic parts that are not a critical part of the perfusion of the donor liver or the overall function of the OCS Liver System.
- One malfunction (Patient (b)(6) occurred during pre-retrieval OCS preparation, when the OCS Liver Perfusion Module electrical connection could not be recognized by the OCS Liver Console. This occurred well before the liver was even surgically retrieved. Thus, the retrieval and preservation proceeded using cold storage.

In the 3 cases where device malfunction was observed, the livers were transplanted, and patient results were analyzed in the OCS Liver PROTECT trial results. The reported malfunctions are summarized in Table 47 below. No corrective actions were required to address any of these malfunctions.

Table 47: Summary of Device Malfunctions in Liver PROTECT trial

Patient	Organ ID	Transplant Date	Malfunction Description	Organ Transplanted?	Recipient Outcome
(b)(6)			SDS Cassette infusion line would not stay connected to the Console. A broken retaining plastic tab was identified on the SDS Cassette. A spare SDS Cassette was used, and the OCS session proceeded without further incident.	Yes, on OCS.	Alive as of Day 394
(b)(6)			Portal vein valve used to flush organ at the end of the OCS perfusion session malfunctioned which resulted in the team flushing directly through the portal vein cannula. The flush proceeded without incident and the liver was transplanted.	Yes, on OCS.	Alive as of Day 382
(b)(6)			Perfusion module was not recognized by the OCS device.	Yes, on ice (patient remained in the trial).	Alive as of Day 345

6.19. Additional Post-hoc Analyses Requested by FDA

In discussions with FDA, TransMedics agreed to perform specific post-hoc analyses of the OCS Liver PROTECT trial data. These are described in the section that follows.

6.19.1. ITT Analyses

FDA requested that TransMedics perform analyses of an "ITT" population, which includes all randomized subjects, regardless of whether they were transplanted and followed in the OCS Liver PROTECT study or not. To address FDA's request, TransMedics obtained follow-up data for the "Transplanted Off Study After Randomization Using Cold Storage" subjects. TransMedics obtained Central IRB approval and requested and obtained graft and patient survival data for these subjects from UNOS/SRTR.

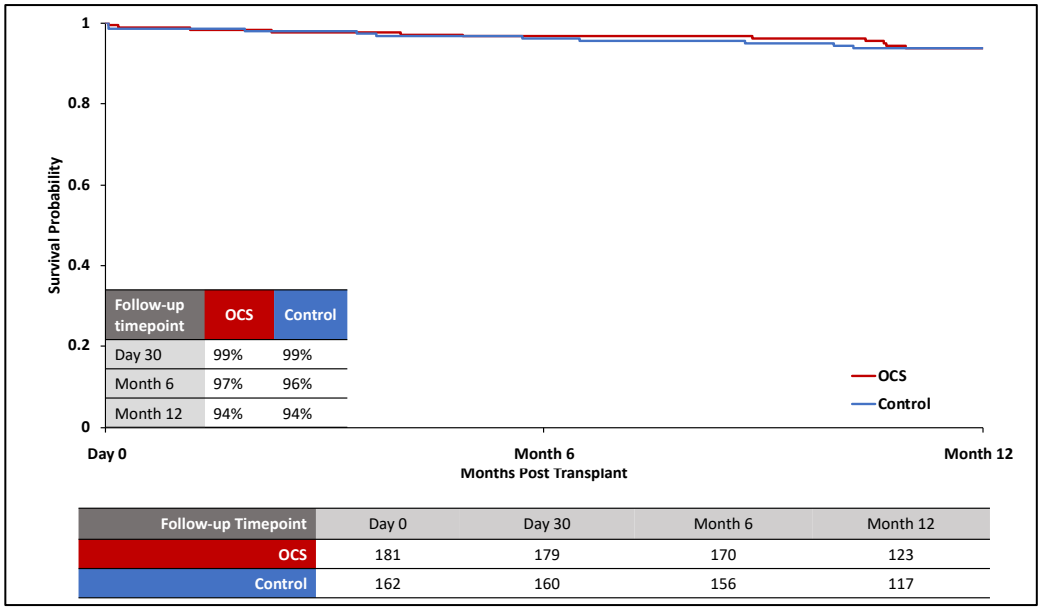
Combining these data with the OCS Liver PROTECT study data, TransMedics performed two analyses as follows:

- The mITT2 population (N=341) consisted of all randomized subjects who were transplanted in either the PROTECT study or outside of the PROTECT study. It included the PROTECT mITT population (N=298) plus an additional 43 subjects who have been transplanted off-study on ice with a randomized organ. Patients were analyzed "as randomized."
- The ITT population (N=343) consisted of subjects who had signed informed consent, been enrolled in the study, randomized, and the assigned liver preservation method had been initiated. It consisted of the PROTECT mITT population (N=298) plus the additional 43 subjects who have been transplanted off-study on ice with a randomized organ, plus two other subjects who were randomized, the preservation method was initiated but the subjects did not receive a transplant. Patient (b)(6) died in the OR without receiving a transplant, and Patient (b)(6) had an organ turndown on OCS and remained in the study and was alive at the end of the study but was still waiting for a liver transplant. Patients were analyzed "as randomized."

Survival for this *post-hoc* ITT population has been updated to include all available data for OCS Liver PROTECT subjects, plus additional survival data for subjects transplanted off-study obtained from SRTR as of November 10, 2020, and for the 2 patients who were never transplanted, the outcomes were imputed.

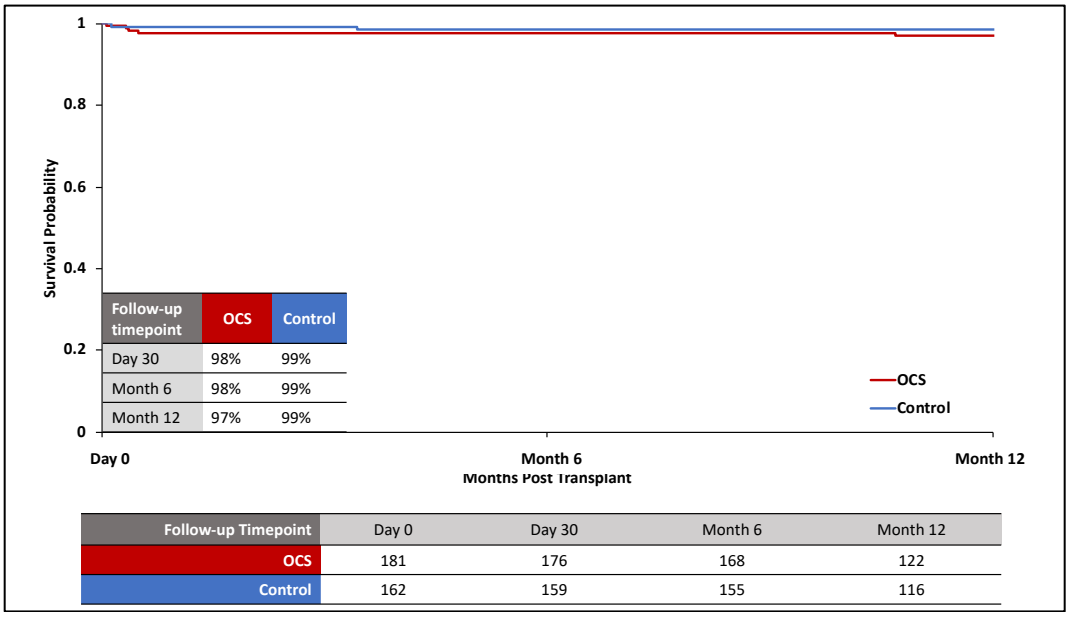
As shown in Figure 47 and Figure 48 below, in the ITT population, there is no difference in patient or graft survival in the OCS and Control arms through 12 months post-transplant.

Figure 47: Kaplan-Meier Recipient Survival (ITT Population)



Follow-up Timepoint	Day 0	Day 30	Month 6	Month 12
OCS	181	179	170	123
Control	162	160	156	117

Figure 48: Kaplan-Meier Liver Graft Survival (ITT Population)



Follow-up Timepoint	Day 0	Day 30	Month 6	Month 12
OCS	181	176	168	122
Control	162	159	155	116

FDA requested an additional analysis of EAD for the ITT population. This information is available for all subjects in the OCS Liver PROTECT trial, but since EAD is not collected in the UNOS database, we were unable to obtain these data for patients transplanted off-study using cold storage. Therefore, multiple imputation (MI) methods were used for patients who were screen failures and were withdrawn and transplanted off study. Using SAS® PROC MI, the logistic regression method of imputation was used with the treatment group and the covariates listed below as explanatory variables.

The following covariates were used to impute missing data outcomes:

- Donor after cardiac death (DCD donor): (Yes, No)
- Donor age: (< 40 years, ≥ 40 years)
- Recipient gender: (Male, Female)
- Recipient age.

Consistent with the results for the PP and mITT populations, the primary effectiveness endpoint analysis of EAD for the ITT population demonstrates statistical non-inferiority and superiority of outcomes of the OCS arm compared to Control. Specifically, the OCS arm had a significant reduction of EAD (18.9%) compared to Control (31.7%), p=0.0101 (Table 48). The tipping point analysis confirmed that the imputation model is robust and provides confirmation of the results (Table 49).

Table 48: Primary Effectiveness Endpoint for ITT Population (Missing Data imputed using Multiple Imputation Methods)

Variable	Statistic	OCS (N=181)	Control (N=162)
Primary effectiveness endpoint: EAD	Estimated Percentage	18.9	31.7
	95% CI for True % [1]	(12.7, 25.2)	(24.2, 39.1)
	Estimated difference in % (OCS - Control)	-0.127	
	95% one-sided upper confidence bound for true difference in proportions (OCS - Control) [2]	-0.046	
	p-value [3]	<0.0001	
	p-value [4]	0.0101	

Note: Results are based on multiple imputation methods for missing data using PROC MI and PROC MIANALYZE of SAS.

(1) Confidence interval for a binomial percentage based on normal approximation.

(2) 95% one-sided upper confidence bound based on normal approximation.

(3) p-value based on a one-sided normal approximation test, testing the null hypothesis that the true OCS proportion is greater than or equal to the true Control proportion + 0.075 vs. the alternative hypothesis that it is less than the true Control proportion plus 0.075.

(4) p-value from a two-sided normal approximation test, testing the null hypothesis that the true difference in proportions equals 0 vs. the alternative hypothesis that it does not equal 0. This will be done only if the null hypothesis of inferiority is rejected.

Table 49: Tipping Point Analysis of Primary Effectiveness Endpoint for ITT Population (Missing Data imputed using Multiple Imputation Methods)

Variable	Shift Number [1]	Statistic	OCS (N=181)	Control (N=162)
Primary effectiveness endpoint: EAD	5	Estimated Percentage (Imputed patients only)	40.8	25.2
		Estimated Percentage (All patients)	21.7	31.7
		95% CI for True % [2]	(15.2, 28.2)	(24.2, 39.1)

Variable	Shift Number [1]	Statistic	OCS (N=181)	Control (N=162)
		Estimated difference in % (OCS - Control)	-0.100	
		95% one-sided upper confidence bound for true difference in proportions (OCS - Control) [3]	-0.017	
		p-value [4]	0.0003	
		p-value [5]	0.0480	

Note: Results are based on multiple imputation methods for missing data using PROC MI and PROC MIANALYZE of SAS.

(1) Shift Number = Number of OCS subjects who were shifted to having EAD after imputed as having no EAD.

(2) Confidence interval for a binomial percentage based on normal approximation.

(3) 95% one-sided upper confidence bound based on the normal approximation.

(4) p-value based on a one-sided normal approximation test, testing the null hypothesis that the true OCS proportion is greater than or equal to the true Control proportion + 0.075 vs. the alternative hypothesis that it is less than the true Control proportion plus 0.075.

(5) p-value based on a two-sided normal approximation.

To summarize, the ITT analyses requested by the FDA lead to the same conclusions as the protocol-specified analyses and support the effectiveness of the OCS Liver System for the proposed clinical indication.

7. OCS LIVER PROTECT CONTINUED ACCESS PROTOCOL (CAP)

The OCS Liver PROTECT Continued Access Protocol (CAP) was approved by FDA on November 14, 2019 under (b) (4) for 74 subjects. The PROTECT CAP is a single-arm study but otherwise the study design was the same as the OCS Liver PROTECT trial. The PROTECT CAP data are provided as a supplemental data set to the PROTECT trial which serves as the primary data set for this PMA.

7.1. CAP Patient Enrollment

A total of 74 subjects have been enrolled in OCS Liver PROTECT CAP. As of the database closure date of April 8, 2021, all 74 subjects have reached 30 days post-transplant, only 50 subjects have reached 6 months, and 19 subjects have reached 12 months. The study is on-going, and data are still being collected, monitored, verified, and adjudicated for all transplanted patients. A summary of the available data for these 74 subjects is provided in the sections that follow.

7.2. Donor Characteristics and Demographics

Donor demographics and characteristics are shown in Table 51 below. There have been no donor liver turndowns after OCS perfusion in the PROTECT CAP. The donor characteristics are similar, except that PROTECT CAP has a higher percentage of DCD donors (23% in CAP) compared to PROTECT (18%). DCD livers are generally considered as higher risk and are associated with higher rates of EAD and graft failure (Lee et al., 2014).

Table 50: Donor Demographic and Baseline Characteristics, OCS Liver PROTECT CAP

Parameter	OCS Patients (N=74)
Age (years): Mean ± SD	57.01 ± 11.572
Gender:	
• Male	56/74 (75.68%)
• Female	18/74 (24.32%)
BMI (kg/m^2): Mean ± SD	29.18 ± 6.258
MELD Score: Mean ± SD	27.69 ± 6.034
Medical history	
• History of diabetes	22/74 (29.73%)
• History of liver cancer	30/74 (40.54%)
Primary Diagnosis	
• Alcoholic Cirrhosis	30/74 (40.54%)
• Cholestatic Diseases	5/74 (6.76%)
• Chronic Hepatitis	12/74 (16.22%)
• Metabolic Diseases	1/74 (1.35%)
• NAFLD/NASH	10/74 (13.51%)
• Primary Hepatic Tumor	13/74 (17.57%)
• Other	3/74 (4.05%)
○ Cholangiocarcinoma	2/74 (2.70%)
○ Primary Biliary Cholangitis	1/74 (1.35%)

7.3. Recipient Demographic and Baseline Characteristics

Recipient demographic and baseline characteristics are shown in Table 51 below and are similar to the OCS Liver PROTECT trial, except that PROTECT CAP has a higher percentage of primary hepatic tumor (17.6% in CAP) compared to PROTECT (9.2%).

Table 51: Recipient Demographic and Baseline Characteristics, OCS Liver PROTECT CAP

Parameter	OCS Patients (N=74)
Age (years): Mean ± SD	57.01 ± 11.572
Gender:	
• Male	56/74 (75.68%)
• Female	18/74 (24.32%)

Parameter	OCS Patients (N=74)
BMI (kg/m^2): Mean ± SD	29.18 ± 6.258
MELD Score: Mean ± SD	27.69 ± 6.034
Medical history	
• History of diabetes	22/74 (29.73%)
• History of liver cancer	30/74 (40.54%)
Primary Diagnosis	
• Alcoholic Cirrhosis	30/74 (40.54%)
• Cholestatic Diseases	5/74 (6.76%)
• Chronic Hepatitis	12/74 (16.22%)
• Metabolic Diseases	1/74 (1.35%)
• NAFLD/NASH	10/74 (13.51%)
• Primary Hepatic Tumor	13/74 (17.57%)
• Other	3/74 (4.05%)
○ Cholangiocarcinoma	2/74 (2.70%)
○ Primary Biliary Cholangitis	1/74 (1.35%)

7.4. Early Allograft Dysfunction (EAD)

EAD for all patients has been adjudicated by the CEC. Nineteen (19) patients experienced EAD within the first 7 days post-transplant, as shown in Table 52 below. The rate of EAD is slightly higher than that observed in the PROTECT trial. The difference in EAD between PROTECT and CAP is not statistically significant (p=0.2178, Fisher's Exact test).

Table 52: EAD Results, OCS Liver PROTECT CAP

	OCS Subjects (N=74)
EAD	19/74 (25.68%)
AST level > 2000 IU/L within the first 7 postoperative days	15/74 (20.27%)
Bilirubin ≥ 10 mg/dl on postoperative day 7	4/74 (5.41%)
INR ≥ 1.6 on postoperative day 7	5/74 (6.76%)
Primary non-functioning graft within the first 7 days	0/74 (0.00%)

7.5. Patient Survival/Graft Survival

By the date of database closure, all 74 patients met the 30-day post-transplant follow-up. The 30-day patient and graft survival were 98.7%. Long-term follow-up of the CAP patients is ongoing. To-date, a total of 5 deaths have occurred among the 74 patients

All of the causes of death and liver graft relatedness have been CEC reviewed and adjudicated. A summary of causes of death are provided in Appendix 4 of this document.

7.6. Device Observations/Complaints

In the OCS Liver PROTECT CAP, there was one device observation that led to retrieval and preservation of the donor liver using standard of care cold storage. After the user primed the OCS and before the liver was instrumented, a "pump failure" message was observed. The liver was not instrumented on the OCS and instead, it was procured and preserved on standard of care cold storage. The recipient was transplanted outside of the trial. The issue was later determined to be related to kinked tubing. This device observation had no impact on the donor liver or the intended recipient.

In addition, there were 2 other complaints in the PROTECT trial. One occurred during routine preventative maintenance and so there was no organ or patient involvement. A third complaint was observed during priming but was corrected and the organ was perfused on OCS and transplanted in PROTECT CAP. This patient was alive with a function graft as of Day 30 post-transplant.

8. OVERALL SUMMARY OF CLINICAL DATA TO SUPPORT APPROVAL OF THE OCS LIVER SYSTEM

The OCS Liver PROTECT trial is a large, multi-center, randomized, controlled trial in the U.S. that was conducted to evaluate the clinical impact of OCS Liver perfusion and assessment on post-transplant clinical outcomes in liver transplantation from DBD and DCD donors. The PROTECT trial results are the primary data set supporting this PMA for the proposed clinical indication.

The results of the OCS Liver PROTECT trial provide ample evidence of effectiveness, safety, and favorable benefit/risk profile to support the OCS Liver System approval for the proposed clinical indication:

OCS Liver System Demonstrated Effectiveness:

- The OCS Liver PROTECT trial met the primary endpoint and demonstrated statistical superiority in reduction of EAD in both PP and mITT populations compared to the Control arm. EAD is the most common severe complication after liver transplantation. EAD is associated with significant risk of graft failure requiring re-transplantation and prolonged ICU and hospital stay, which negatively impact patients' clinical quality of life and healthcare resource utilization post-transplant.
- The OCS Liver PROTECT trial met all secondary effectiveness endpoints demonstrating that liver grafts can be assessed and monitored extracorporeally using the OCS Liver System.

- The use of the OCS Liver System demonstrated a clinically significant reduction of the most serious long-term post-transplant complication of ischemic biliary complications compared to Control at the 6 and 12-month follow-up timepoints in both the PP and mITT populations. Ischemic biliary complications negatively impact long-term viability of the liver allograft and patient survival.
- The use of OCS Liver System resulted in significant reduction of ischemic time on the donor liver which resulted in less ischemia/reperfusion (IR) injury in the OCS arm compared to Control based on blinded pathological assessment.
- The OCS livers were associated with high and comparable patient survival at 30 days, at initial hospital discharge, and at 6 and 12 months compared to the Control arm.
- The results of the OCS Liver PROTECT CAP provide additional supporting evidence of the effectiveness of the OCS Liver System to preserve livers (including DCD livers) with a lower rate of EAD compared to Control arm of PROTECT.

OCS Liver System Demonstrated Safety:

- The OCS Liver PROTECT trial met its safety endpoint by demonstrating that the average rate of LGRSAEs in the OCS arm was statistically non-inferior to the Control arm.
- When analyzing the specific LGRSAEs, the OCS arm did not experience any ischemic biliary complications in the first 30 days post-transplant and was associated with lower incidence of vascular complications compared to Control arm.
- Rate of reported device malfunctions was low. Importantly, all 3 donor livers in these reported cases of device malfunction were transplanted and analyzed successfully in the results of the OCS Liver PROTECT trial. There was no increased risks or additional risks observed to donor organs or recipients as a result of these reported incidents.
- There were no safety signals seen in patient mortality, graft survival, or LGRSAEs. Serious Adverse Events (SAEs) were those typically experienced post-liver transplant and were similar for the OCS and Control groups.

The OCS Liver System Demonstrated Favorable Public Health Benefit/Risk Profile by:

- Positively impacting DBD and DCD donor liver utilization for transplantation
- Significantly improving post-transplant clinical outcomes

Clinical benefits associated with OCS Liver positive impact on DBD and DCD donor organ utilization for transplantation:

- The OCS Liver System significantly reduced ischemic injury/time on donor livers despite long out of body time. This capability may potentially enable safe distant liver procurement to maximize utilization of the donor liver allografts from both DBD and DCD donors
- OCS Liver System's assessment capabilities resulted in two distinct potential clinical benefits in liver transplantation:
  - Substantial increase in DCD donor liver utilization for transplantation (i.e. OCS 28/55 (51%) vs. Control 13/51 (26%));

- It enabled more clinical datapoints to be evaluated *ex-vivo* that may have assisted in the identification of hidden pathologically damaged DCD liver allografts, protecting the intended recipients from potentially poor outcomes.

Broader utilization of DBD and DCD livers for transplantation in the U.S. would be a substantial clinical public health benefit to meet the growing demand for liver transplant therapy and could potentially reduce the waiting list mortality for patient waiting for a liver transplantation.

Clinical benefits associated with OCS Liver improved post-transplant clinical outcomes:

- The use of the OCS Liver System was associated with significant reduction in incidence of EAD post-liver transplantation. The data in the PROTECT trial as well as studies in the literature demonstrate that the reduction of EAD is associated with:
  - Significant reduction in risks for post-transplant graft failure;
  - Significant reduction of post-transplant ICU and hospital length of stay of transplant recipients;
  - Significant reduction of liver allograft ischemia/reperfusion injury based on histological assessment; and
  - Significant reduction in post-transplant reperfusion syndrome for transplant recipients as assessed by recipients' lactate levels post-transplantation.
- The use of the OCS Liver System was also associated with clinically significant reduction of ischemic biliary complications at 6 and 12 months post-transplant.
- There were no safety signals with a low number of LGRSAEs

Improved clinical outcomes after liver transplantation would be a significant public health benefit as it would make liver transplant outcomes more successful while potentially reducing post-transplant healthcare resource utilization.

In conclusion, the OCS Liver PROTECT trial was the first of its kind trial to target a specific group of DBD and DCD liver donors that may be challenging to utilize with cold storage. Achieving the above superior clinical effectiveness and safety outcomes should enable expansion of donor liver utilization from DBD liver allografts and expansion of the donor pool by using DCD liver allografts to help end-stage liver failure patients access this curative transplant therapy.

9. 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 Liver 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 Liver System. An overview of the training program is provided in the sections that follow.

9.1. 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 livers, to simulate the clinical use of the OCS Liver System.

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

9.2. 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 Liver 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
- Liver 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 Liver training and support application that includes step by step instructions of the use model for OCS Liver System, as well as training videos/materials for immediate access. TransMedics maintains 24/7 phone support for all users.

10. POST-APPROVAL STUDY

TransMedics recognizes the value of collecting post-approval and longer-term data for the OCS Liver technology. TransMedics has proposed continued follow-up of subjects in the OCS Liver PROTECT trial (both OCS and Control) for up-to 2 years, as well as continued follow-up for up to 2 years for the patients enrolled in the OCS Liver PROTECT CAP, giving a total of 374 patients in the PAS.

The OCS Liver System is a preservation technology to reduce ischemia/reperfusion injury on the donor liver and provides *ex vivo* assessment of donor liver function to potentially increase clinical confidence in the donor graft for transplantation. The clinical impact of preservation technology like the OCS is most relevant in the immediate post-transplant period. We have proposed follow-up of up-to 2 years which is more than adequate clinically. A longer term follow-up would be heavily confounded by different clinical variables like immunosuppressive compliance and patients' overall health status etc. Thus, we strongly believe that our proposal to collect data for 2 years on the OCS Liver PROTECT trial patients would be clinically robust.

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12. APPENDIX 1: PRINCIPLES OF OPERATION/CLINICAL USE

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

12.1. Preparation and Connection of the Donor Liver to the OCS Liver System

12.1.1. Pre-Retrieval Readiness

An OCS retrieval bag, which contains all supplies necessary for donor liver retrieval, is assembled prior to use. If the donor liver offer is accepted, the team begins routine OCS Liver System checks to insure preparedness for use. During this time, the team will check batteries and gas tank supply. The LvPM is supplied pre-assembled, and the team inserts the LvPM into the Liver 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 LvPM.

12.1.2. Prime System with Blood and Fluids

The OCS Liver System is primed with (b) (4) through prime lines. The priming components are mixed by starting the Console pump, which also provides perfusate flow through the circuit to prime and de-air the LvPM. Starting the pump will automatically activate gas flow and blood warming. The user adds the recommended additives into the perfusate through the reservoir injection port.

SDS infusions initiated with the pump start include (b)(4) and the reconstituted OCS Liver Bile Salts.

12.1.3. Instrumentation of Donor Liver

The donor liver is flushed and harvested from the donor according to standard clinical practice. Once the liver is removed, it must be prepared for instrumentation on the OCS Liver System.

The Hepatic Artery (HA), Portal Vein (PV), Common Bile Duct, and Inferior Vena Cave (IVC) are cannulated. The donor liver is flushed again before instrumenting into the OCS Liver System. The donor liver is placed in the organ chamber of the LvPM. The HA and PV cannulae are connected to the LvPM HA and PV ports. The pump flow is started. The IVC Cannula is directed to the drainage area. The Bile Cannula is connected to the bile drainage port.

12.2. Maintenance and Transportation of the Donor Liver

The OCS is used to maintain and protect the donor liver during transportation. Pump flow and solution infusion rates are set to optimize the Hepatic Artery Flow (HAF), Portal Vein Flow (PVF), Hepatic Artery Pressure (HAP), and Portal Vein Pressure (PVP), perfusate temperature, oxygen gas flow, and circulating arterial lactate trend. Determination of arterial lactate values are used to confirm adequacy of perfusion of the liver. The OCS can be operated by either external AC power or internal batteries. During transport and throughout the preservation session, the Wireless Monitor will display a number of parameters, including Hepatic Artery

Flow (HAF), Portal Vein Flow (PVF), oxygen saturation (SvO_2), hematocrit (HCT), temperature, Hepatic Artery Pressure (HAP), and Portal Vein Pressure (PVP) levels.

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

12.3. Evaluation and Transplantation

12.3.1. Evaluate Liver

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

12.3.2. Prepare Recipient

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

12.3.3. Flush Liver

The donor liver is flushed and cooled on the OCS Liver System at the end of the perfusion session, using cold flush solution.

12.3.4. Remove Liver from System

The LvPM organ chamber is opened. The HA and PV Cannulae are clamped and then disconnected. The IVC and Bile Cannulae are disconnected. The donor liver is then removed from the LvPM organ chamber and prepared for transplantation in accordance with standard surgical procedures.

12.3.5. Transplant into Recipient

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

12.3.6. Post-Device Use

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

13. 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 Liver System. These data have been reviewed by FDA and all outstanding issues and questions have been addressed.

13.1. Engineering Bench Testing

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

Table 53 below identifies the engineering bench testing performed on the OCS Liver System for which we are seeking PMA approval. The testing was performed at the system level, on the OCS Liver System, as well as on the components that comprised of the system, including the Liver Console and LvPM. Given the commonality of the OCS platform, some of the testing was performed on the OCS Heart or OCS Lung; however, TransMedics provided rationales in the PMA application why the results were applicable.

Table 53: Summary of Bench Testing

Test	Conclusion
OCS System Shock and Vibration Testing	The system performed to specification when exposed to levels of mechanical shock and vibration consistent with those anticipated during transport and extended use.
OCS System Operational Temperature and Humidity Testing	The 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 System Operational Altitude Testing	The system performed to specification when exposed to levels of altitude expected during OCS use.
OCS Operational System Driven Rain Test	This test verified that, after simulating transport 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.
OCS Console Mechanical Design Verification	The mobile base and the basic attributes of the Wireless Monitor met the specified mechanical requirements for use.
Mechanical Functionality Test	The system met its physical and mechanical performance requirements.
System PCBAs Electrical Test	TransMedics manufacturing processes include adequate tests to verify that the electrical systems are free from functional defects.
OCS Console Battery Pack Life Cycle Test	The OCS Console Battery packs met all specifications through their expected life and are acceptable for use in the 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
SvO_2/HCT Probe Accuracy Test	The probe that measures oxygen saturation and Hematocrit is acceptable for use in the specified ranges of HCT and SvO_2.
Console Bluetooth Serial Adapter Performance Verification	The Console Bluetooth module met the system product requirements for wireless communication and range.
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.
Console Flowmeter Board Verification	The boards in the Console that are used to measure perfusate flow in the Perfusion Module met the OCS product requirements with respect to flow rate range and accuracy.
Console Gas Cylinder Retention Strap Verification	The verification proved proper fit and retention of gas cylinder within the Console's gas cylinder compartment.
Perfusion Module Front End Board Verification	This test verified that the Printed Circuit Board Assembly (PCBA) on the Perfusion Module Front End Board met product requirements.
Perfusion Module 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 Perfusion Module.
Perfusion Module Filter Defoamer Challenge Test	The Perfusion Module met the product requirements with regards to the defoamer.
Performance Testing of the Novalung Oxygenator	The oxygenator was verified to meet the Performance Module performance specifications.
Perfusion Module Pressure Transducer Accuracy Verification	This test verified the accuracy of the pressure transducer used on the Perfusion Module.
Tensile Strength of Perfusion Module Tubing Connections	The results demonstrate the tensile and mechanical integrity of all Perfusion Module tubing and connectors used to transport perfusate or gas.

13.2. Biocompatibility Testing

TransMedics performed a series of biocompatibility studies to demonstrate the safety, suitability, and compatibility of the materials of the LvPS, which consists of the LvPM and LvPS 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 LvPS 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 54 below.

Table 54: 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

13.3. Biological Safety of the OCS Liver Bile Salts Set

To support the biological safety of Sodium Taurocholate (OCS Liver Bile Salts), TransMedics provided the information consistent with the FDA guidance entitled, "Medical Devices Containing Materials Derived from Animal Sources (Except for In Vitro Diagnostic Devices)." This information included the control of animal tissue collection, manufacturing controls, the assessment for need for virus validation studies, and the exposure to Transmissible Spongiform Encephalopathies (TSE) risk.

13.4. Software Verification and Validation Testing

TransMedics performed system level software verification and validation testing to demonstrate the OCS Liver 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.

13.5. 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 Liver System incorporates a Wireless Monitor dedicated to the Liver 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.

13.6. Electrical and Medical Device Safety

The OCS Liver 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 Liver System met the requirements of the standards. Results are shown in Table 55 below.

Table 55: 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
Hazardous Situations and Fault Conditions	13	Pass
Programmable Electrical Medical Systems (PEMS)	14	Pass
Construction of ME Equipment	15	Pass
ME Systems	16	Pass

13.7. Electromagnetic Compatibility (EMC)

The OCS Liver 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 Liver System met the requirements of the standards. Results are shown in Table 56 below.

Table 56: 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

13.8. 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.”

13.9. Sterilization

The LvPS 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 Liver Bile Salts are sterilized by gamma irradiation. The sterilization cycle was validated to achieve a minimum SAL of 10^{-6} in accordance with EN ISO 11137-2:2013.

13.10. Shelf Life Testing

Package integrity and simulated shipping testing was performed for the LvPS and OCS Liver Bile Salts 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 LvPS OCS Liver Biles Salts Set for their respective labeled shelf life.

13.11. Animal Functional Testing

TransMedics performed multiple functional animal studies to evaluate the safety, suitability, and effectiveness of the OCS Liver System for the preservation of donor livers. The animal studies were performed at TransMedics' dedicated animal laboratory, located at (b)(4) , which complies with the USDA regulations promulgated under the Animal Welfare Act. The studies were conducted in accordance with established scientific principles, using protocols and standard, written methods with prospectively identified acceptance criteria. The studies were performed by trained and experienced personnel.

The animal studies performed are summarized in Table 57 below and as shown in the table, they included studies of 44 swine livers preserved on OCS. Several studies with performed with cold storage controls and histopathological analysis which showed improved hepatocellular and hepatobilary structure as compared to control. The extensive pre-clinical animal testing supported the safety of the OCS Liver System for use in clinical studies and laid the foundation for TransMedics to design the PROTECT trial to use lactate levels throughout OCS Liver perfusion (every ~2 hours), as well as liver enzymes at the beginning and end of OCS perfusion, and bile production to assess liver function.

Table 57: Summary of Animal Functional Studies

OCS Liver Preclinical Study	Number of Animals	Summary Results
Phase 1: Up to 12-hour preservation on OCS Liver System	OCS N=28	Stable preservation with good liver hepatocellular, hepatobiliary, metabolic, and synthetic function.
Phase 2: 8-hour preservation followed by 4 hours of simulated transplantation	OCS N=5	The OCS Liver met the prespecified acceptance criteria and demonstrated stable perfusion and metabolic parameters.

OCS Liver Preclinical Study	Number of Animals	Summary Results
Phase 2 expanded: 8-hour preservation followed by 4 hours of simulated transplantation with control	OCS N=6 vs. Control N=6	OCS arm showed better recovery of function as compared to Cold Storage Control arm. In addition, histology results showed better preserved hepatocellular and hepatobiliary structure as compared to Controls.
Phase 3: 12-hour preservation followed by 24 hours of simulated transplantation	OCS N=3 vs. Control N=3	OCS arm showed better recovery of function as compared to Cold Storage Control arm. In addition, histology results showed better preserved hepatocellular and hepatobiliary structure for OCS as compared to Controls.
Preclinical Validation Study to validate OCS Liver with Software Version 3.2.1-C	OCS N=2	The OCS Liver System met all the acceptance criteria for this validation.

14. APPENDIX 3: OCS LIVER PROTECT TRIAL SUMMARY OF CAUSES OF DEATH

All reported deaths that occurred in the OCS Liver PROTECT trial have been reviewed and adjudicated by the Clinical Events Committee. A summary of the deaths that occurred through the study follow-up period reported in the PMA are provided in Table 58.

Table 58: Summary of Deaths in the OCS Liver PROTECT Trial

Patient ID	Arm	Is the Death Liver Graft-related?	Trial Day	CEC-adjudicated Cause of Death	Circumstances of Death
(b)(6)	OCS	No	0	Cardiac arrest during transplant procedure due to intracardiac thrombosis	Recipient was a transplant candidate due to liver failure from hepatitis C, decompensated HCV and hepatopulmonary syndrome, MELD score 27. Patient died on day 0 post-transplant from cardiac arrest during transplant procedure due to intracardiac thrombosis following hypercoagulation in early post implantation period. CEC adjudicated cause of death as not liver graft-related.
(b)(6)	OCS	No	34	Severe respiratory failure	Recipient was a transplant candidate due to liver failure from cryptogenic cirrhosis complicated by hepatopulmonary syndrome, MELD score 25. Patient with a history of hepatopulmonary syndrome died on day 34 post-transplant from severe respiratory failure. Subject did not experience early allograft dysfunction. Severe respiratory distress syndrome started on day 8 post-transplant which the subject did not recover from despite treatment with mechanical ventilation and ECMO. CEC adjudicated cause of death as not liver graft-related.
(b)(6)	OCS	No	122	Sepsis	Recipient was a transplant candidate due to liver failure from alcoholic cirrhosis and liver cancer, MELD score 29. Patient died on day 122 post-transplant from sepsis. Patient was initially discharged on day 6 post-transplant, but readmitted about two months later for treatment of infection. Died in hospital following a number of critical events requiring aggressive treatment. CEC adjudicated cause of death as not liver graft-related.
(b)(6)	OCS	No	148	Metastatic angiosarcoma[3]	Recipient was a transplant candidate due to liver failure from cryptogenic cirrhosis, MELD score 42. Patient died on day 148 post-transplant from metastatic angiosarcoma. Patient's native

Patient ID	Arm	Is the Death Liver Graft-related?	Trial Day	CEC-adjudicated Cause of Death	Circumstances of Death
					liver was found to have hepatic sarcoma. Patient was initially discharged 14 days post-transplant but readmitted on day 25 post-transplant due to failure to thrive followed by deep vein thrombosis and pulmonary embolism. Clinical evaluation showed evidence of cancer with numerous metastases. Patient decompensated after two chemotherapy treatments. CEC adjudicated cause of death as not liver graft-related.
(b)(6)	OCS	No	269	Metastatic hepatocellular carcinoma[3]	Recipient was a transplant candidate due to liver failure from HCC, MELD score 15. Patient died on day 269 post-transplant from metastatic hepatocellular carcinoma. The patient was initially discharged 77 days post-transplant following a protracted post-operative course complicated by multiple serious adverse events including pulmonary embolism, liver allograft torsion, and ARDS. During clinical evaluation, metastatic hepatocellular carcinoma was diagnosed weeks before patient's death. CEC adjudicated cause of death as not liver graft-related.
(b)(6)	OCS	No	316	Metastatic hepatocellular carcinoma[3]	Recipient was a transplant candidate due to liver failure from cryptogenic cirrhosis and liver cancer, MELD score 30. Patient died on day 316 days post-transplant from metastatic hepatocellular carcinoma. The patient was initially discharged 14 days post-transplant. Patient was diagnosed with metastatic hepatocellular carcinoma at home and died in hospice. CEC adjudicated cause of death as not liver graft-related.
(b)(6)	OCS	No	324	Sepsis	Recipient was a transplant candidate due to liver failure from chronic hepatitis C, MELD score 39. Patient died on day 324 post-transplant from sepsis. Patient was initially discharged 13 days post-transplant. Following initial hospital discharge, patient had multiple re-hospitalizations. He was diagnosed with sepsis and failure to thrive during his last re-hospitalization. Died in home hospice. CEC adjudicated cause of death as not liver graft-related.

Patient ID	Arm	Is the Death Liver Graft-related?	Trial Day	CEC-adjudicated Cause of Death	Circumstances of Death
(b)(6)	OCS	Yes	325	Multi system organ failure	Recipient was a transplant candidate due to liver failure from chronic hepatitis C, MELD score 32. Patient died on day 325 post-transplant from multi system organ failure. Patient was initially discharged 10 days post-transplant. Following initial hospital discharge, patient was re-hospitalized for jaundice and later for cellulitis. Liver function further deteriorated, family elected DNR status and patient died in hospital. CEC adjudicated cause of death as liver graft-related.
(b)(6)	OCS	NA	333	Unknown	Recipient was a transplant candidate due to liver failure from alcoholic hepatitis, MELD score 20. Patient died on day 333 post-transplant; cause of death is unknown. The patient was initially discharged home 5 days post-transplant. Recipient was found dead at home. Family ceased the contact with transplant hospital; therefore, cause of death is unknown. CEC was unable to adjudicate whether death was liver graft-related or not.
(b)(6)	OCS	Yes	444	Liver failure due to rejection	Recipient was a transplant candidate due to liver failure from alcoholic cirrhosis, MELD score 17. Patient died on day 444 post-transplant from liver failure due to rejection. The patient was initially discharged 15 days post-transplant. Acute rejection was diagnosed over a year post-transplant. Despite the treatment, rejection progressed to chronic, with marked cholestasis on biopsy. Treatments were stopped due to poor prognosis; patient died in hospice. CEC adjudicated cause of death as liver graft-related.
(b)(6)	OCS	No	630	Recurrent hepatocellular carcinoma (HCC) with metastases in lungs and spine	Recipient was a transplant candidate due to liver failure from hepatitis B with HCC, MELD score 17. The recipient died 630 days post-transplant from recurrent HCC with metastases in lungs and spine. The patient was initially discharged 4 days post-transplant. Ischemic biliary stricture was diagnosed and treated with stenting approximately 10 months later. CEC adjudicated cause of death as not liver graft-related.
(b)(6)	Control	N/A	0	Cardiac arrest during transplant	Recipient was a transplant candidate due to liver failure from hepatitis C and HCC, MELD score 35.

Patient ID	Arm	Is the Death Liver Graft-related?	Trial Day	CEC-adjudicated Cause of Death	Circumstances of Death
				procedure due to intracardiac thrombosis	Patient died on the operating room table, in pre-implant period from cardiac arrest due to intracardiac thrombosis. Hence, liver graft-relatedness does not apply.
(b)(6)	Control	No	0	Cardiac arrest during transplant procedure due to intracardiac thrombosis	Recipient was a transplant candidate due to liver failure primary biliary cirrhosis, MELD score 20. Patient died on day 0 post-transplant from cardiac arrest due to intracardiac thrombosis; death occurred in early post implantation period. CEC adjudicated cause of death as not liver graft-related.
(b)(6)	Control	No	57	Acute graft-versus-host disease (GVHD) of the gut and skin	Recipient was a transplant candidate due to liver failure from cryptogenic cirrhosis, MELD score 27. Patient died on day 57 post-transplant from acute graft versus host disease of the gut and skin. The patient was initially discharged 8 days post-transplant but readmitted about a month after transplant with GVHD symptoms. Died in hospital following readmission. CEC adjudicated cause of death as not liver graft-related.
(b)(6)	Control	Yes	104	Cardiogenic shock and septic shock	Recipient was a transplant candidate due to liver failure from HCC, MELD score 29. Patient died on day 104 post-transplant from cardiogenic shock and septic shock. The patient was initially discharged 11 days post-transplant, but readmitted around 3 months after for treatment of infection Patient decompensated despite treatment and died in hospital. CEC adjudicated cause of death as liver graft-related.
(b)(6)	Control	No	112	Acute hypoxia	Recipient was a transplant candidate due to liver failure from alcoholic cirrhosis, MELD score 32. Patient died on day 112 post-transplant from acute hypoxia. The patient suffered a complex post-transplant course and was never discharged from ICU, post-transplant period was complicated by multiple serious adverse events, with respiratory failure and atrial fibrillation contributing to death. CEC adjudicated cause of death as not liver graft-related.
(b)(6)	Control	No	173	Sepsis	Recipient was a transplant candidate due to liver failure from chronic hepatitis C, HCC and alcoholic cirrhosis, MELD score 27. Patient died on day 173 post-transplant from sepsis. He was

Patient ID	Arm	Is the Death Liver Graft-related?	Trial Day	CEC-adjudicated Cause of Death	Circumstances of Death
					discharged 17 days after transplant. Initial post-transplant was significant for ischemic biliary strictures that was ongoing at the time of death. Patient was readmitted to hospital in December (approximately 5 months after transplant) for confusion, shortness of breath. Head CT showed generalized infectious process. Treatment was ineffective and patient died in hospital ICU.
(b)(6)	Control	No	197	Cardiac arrest	Recipient was a transplant candidate due to liver failure from alcoholic cirrhosis, MELD score 20. Patient died on day 197 post-transplant from cardiac arrest. The patient was initially discharged 12 days post-transplant. Patient had multiple readmissions for treatment of graft rejection, infection and preexisting cardiac conditions. Died during the last hospital readmission for elevated enzymes evaluation. CEC adjudicated cause of death as not liver graft-related.
(b)(6)	Control	No	266	ARDS	Recipient was a transplant candidate due to liver failure from hepatitis C cirrhosis and HCC, MELD score 34. Patient died on day 266 post-transplant from acute respiratory distress syndrome. The patient was initially discharged 6 days post-transplant. Patient died in hospital, ARDS was precipitated by sepsis and pneumonia. CEC adjudicated cause of death as not liver graft-related.
(b)(6)	Control	No	303	Suicide	Recipient was a transplant candidate due to liver failure from alcoholic cirrhosis, MELD score 33. Patient died on day 303 post-transplant from suicide. The patient was initially discharged 19 days post-transplant. Patient had delirium in early post-transplant period and was treated with an antipsychotic for 6 months. CEC adjudicated cause of death as not liver graft-related.
(b)(6)	Control	No	311	Sepsis	Recipient was a transplant candidate due to liver failure from alcoholic cirrhosis, MELD score 32. Patient died on day 311 post-transplant from sepsis. The patient was initially discharged 5 days post-transplant. Patient started using alcohol again, eventually she was admitted with

Patient ID	Arm	Is the Death Liver Graft-related?	Trial Day	CEC-adjudicated Cause of Death	Circumstances of Death
					cough and fever and treated for infection and hypotension; due to unfavorable prognosis she was made DNR and died the next day. CEC adjudicated cause of death as not liver graft-related.
(b)(6)	Control	No	558	Unknown[4]	Recipient was a transplant candidate due to liver failure from HCC, MELD score 27. Patient died on day 558 post-transplant in hospice care in another state; medical records could not be obtained and, therefore, cause of death is unknown. The patient was initially discharged 4 days post-transplant. Patient had fungal peritonitis and suffered from stroke. He was admitted to hospice after subsequent stroke, recurrent pneumonia infections related to aspiration, G-tube complications, and bacteremia. CEC adjudicated death as not liver graft-related.

(1) Patient (b)(6) died in the OR prior to transplant. NOTE: this subject is not included in any K-M patient survival curves
(2) Patient (b)(6) was found dead at home; no information on cause of death could be obtained.
(3) This patient had a past medical history of liver cancer, and in the case of (b)(6) native liver pathology showed hepatic sarcoma.
(4) Patient died in hospice, the reported the cause of death as "Unknown" due to the inability to obtain the medical records to ascertain the cause of death

15. APPENDIX 4: OCS LIVER PROTECT CAP SUMMARY OF CAUSES OF DEATH

All reported deaths that occurred in the OCS Liver PROTECT CAP trial have been reviewed and adjudicated by the Clinical Events Committee. A summary of the deaths that occurred through the study follow-up period reported in the PMA are provided in Table 59.

Table 59: Summary of Deaths in the OCS Liver PROTECT CAP

Subject ID	Days After Transplant[1]	Is the Death Liver Graft-related?	CEC Adjudicated Cause of Death	Circumstances of Death
(b)(6)	30	No	Sepsis secondary to perforated duodenal ulcer	Patient was treated for perforated duodenal ulcer in post-transplant period and died from its complications resulting in sepsis
(b)(6)	59	No	Sepsis most likely originating from the lungs	Patient was treated for pseudomonas infection and polymicrobial blood stream infection and died from sepsis most likely originating in lungs, as the patient was intubated prior death
(b)(6)	75	No	Respiratory failure from pre-existing hepatopulmonary syndrome	Patient had a pre-existing hepatopulmonary syndrome leading to respiratory failure post-transplant
(b)(6)	108	No	Mycobacterium lung abscess secondary to respiratory failure and lung infection	Patient's post-transplant course was complicated with respiratory failure and subsequent lung infection, Mycobacterium growth was confirmed with left lower lobe entrapment
(b)(6)	111	NA (patient died with re-transplanted liver preserved on cold storage)	Sepsis (after retransplant with liver preserved with cold storage)	Patient suffered cardiac arrests during transplant surgery pre-implantation leading to allograft failure of the first liver and respiratory failure. Following liver retransplant with the liver preserved with cold storage, patient suffered from multiple infections resulting in death from sepsis

(1) Death day =death date-transplant date+1