SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Ex Vivo Portable Organ Perfusion System for Donor Livers
Device Trade Name:	OCS Liver System
Applicant's Name and Address:	TransMedics, Inc. 200 Minuteman Road, Suite 302 Andover, MA 01810
Premarket Approval Application (PMA) Number:	(b) (4)
Date(s) of Panel Recommendation:	N/A
Date of Good Manufacturing Practice Inspection:	September 15-18, 2020
Date of Notice of Approval to the Applicant:	TBD

II. INDICATIONS FOR USE

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.

III. CONTRAINDICATIONS

The OCS™ Liver System should not be used for:

- Livers with moderate or severe traumatic injury
- Livers with active bleeding (e.g., hematomas)
- Split livers.

IV. WARNINGS AND PRECAUTIONS

Refer to the labeling for applicable warnings and precautions.

V. DEVICE DESCRIPTION

The **OCS Liver System** is an integrated portable platform designed to maintain donor livers in a near-physiologic, normothermic, and perfused state. The OCS Liver System is comprised of three major components as described below.

OCS Liver Console (Liver Console): This is a compact electromechanical device that contains an integrated pulsatile perfusion pump, batteries, perfusate warmer, and pressure, flow, and saturation meters. In addition, it has an integrated Wireless Monitor that allows the clinical operator to control and display critical perfusion parameters of the preserved donor livers.

OCS Liver Perfusion Set (LvPS): The LvPS consists of the Liver Perfusion Module (LvPM) and LvPS Accessories.

- The LvPM is a sterile, single-use perfusion module that maintains the organ's physiologic environment and has embedded sensors to optimize and monitor the perfusion parameters and bile production. In addition, the perfusion module enables perfusate sampling in order to monitor the liver's metabolic condition.
- The LvPS Accessories are sterile, disposable accessories necessary to instrument the liver and manage the 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.

OCS Liver Bile Salts Set: The OCS Liver Bile Salts are 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.

These three major components are shown in Figure 1 below.

Figure 1: Components of the OCS Liver System

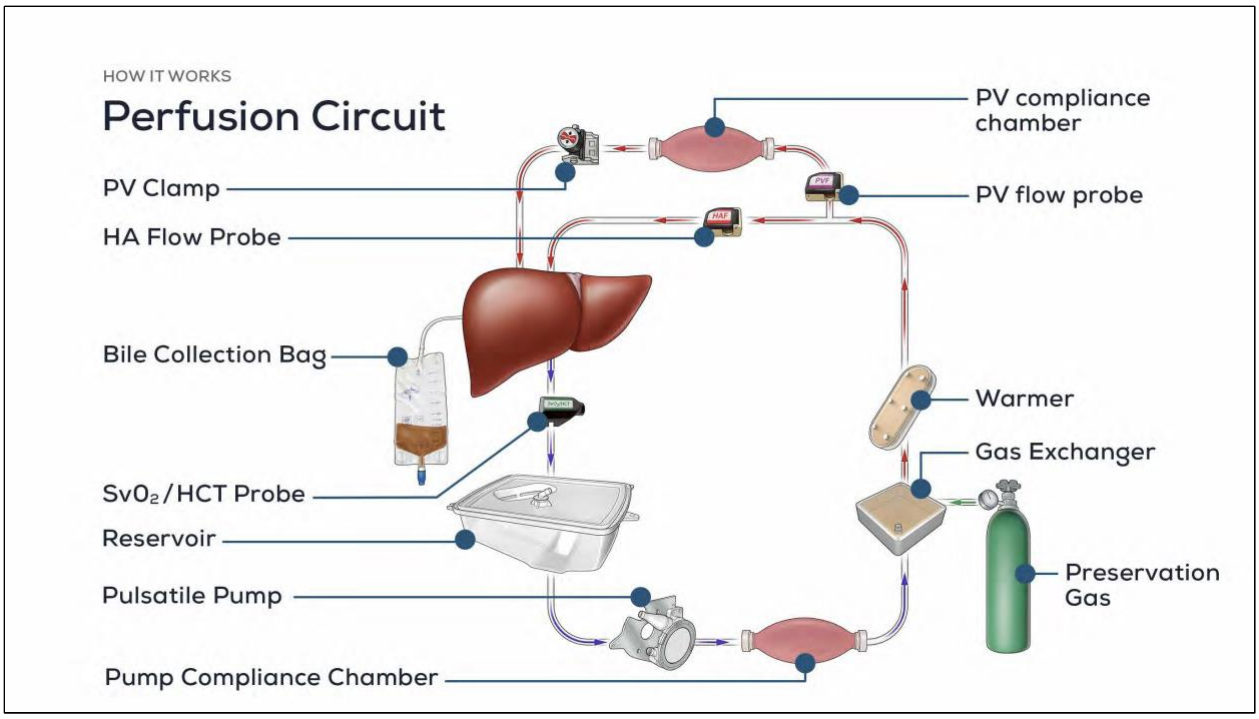
OCS Liver Console	OCS Liver Perfusion Set	OCS Liver Bile Salts
		

Note: The Liver Console figure (left) shows the LvPM mounted into the system. The LvPS figure (middle) only shows the LvPM.

The OCS Liver System preserves the liver in a near-physiological, functioning state by perfusing the liver with a continuously-circulating mixture of warm pRBC-based perfusate supplemented with nutrients and oxygen in a controlled and protected environment referred to as the circuit. The perfusate consists of user-supplied multiple-electrolytes solution (PlasmaLyte® or equivalent), Albumin, pRBCs, and other additives.

Figure 2 below illustrates the circulation of perfusate through the LvPM circuit. The perfusate is pumped from the reservoir by the Circulatory Pump (labeled as the pulsatile pump 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 2: Schematic of OCS Liver System Fluid Flow



To adequately maintain the liver, the OCS Liver System controls and monitors the preservation environment. The user can adjust the 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.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Liver transplantation is the only curative treatment for end stage liver failure. Without a liver transplant, 22% of patients will die or become too ill to be transplanted within one year of being on the waiting list (Kim, et al., 2019).

Standard of care preservation for donor livers is cold, static storage of the donor liver in a commercially available hypothermic preservation solution prior to transplantation. There are no other legally-marketed devices in the U.S. that are designed to provide donor liver preservation in a near physiologic, normothermic, and perfused state.

VII. MARKETING HISTORY

The Liver Console and Liver Perfusion Set (LvPS) have CE mark authorization, but the OCS Liver System has not been commercially distributed in the EU or around the world.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Liver transplant patients, regardless of the method of donor organ preservation, may experience any of the following adverse events.

- Acute rejection
- Atrial and ventricular arrhythmias
- Bleeding
- Hemodynamic instability
- Death
- Fever
- Early liver allograft dysfunction (EAD)
- Respiratory failure
- Liver primary non-function
- Bile leaks
- Hepatic artery thrombosis
- Portal vein thrombosis
- Cholangitis
- Liver abscess
- Diaphragmatic injury
- Phrenic nerve injury
- Sepsis
- Renal dysfunction and/or failure
- Hyperammonaemia
- Malignancy (post-transplant lymphoproliferative disorder (PTLD)
- Multiple organ failure
- Myocardial infarction
- Neurological dysfunction
- Hepatic dysfunction
- Pancreatitis
- Peptic ulceration
- Gastritis
- Gastro esophageal reflux disease (GERD)
- Aspiration
- Cardiac tamponade
- Pneumo-mediastinum
- Pneumothorax
- Hemothorax
- Ascites
- Pleural effusion
- Venous thromboembolism (deep venous thrombosis [DVT])
- Pulmonary embolism (PE)
- Abdominal wound dehiscence
- Organ deemed not transplantable after retrieval
- Stroke
- Psychosis
- Ileus
- Bowel obstruction
- GI Bleeding (upper or lower)
- Cerebrovascular accident
- Peripheral vascular clotting or occlusion due to insertion of mechanical support or equivalent
- Delirium, confusion and neurological complications
- Hepatic coma
- Retransplantation
- Limb gangrene due to vascular occlusion due to insertion of mechanical support
- Use of mechanical circulatory support
- Coagulopathy
- Blood product transfusion
- Transfusion reaction
- Hyperacute rejection
- Anastomotic site complications; narrowing, bleeding or occlusion
- Bowel thromboembolic complications and gangrene
- Protamine and other anti-heparin medication reaction
- Heparin induced thrombocytopenia
- Anemia
- Atrial fibrillation
- Biliary complication (Ischemic and non-ischemic and bile leak)
- Hepatic artery stenosis
- Convulsion
- Diabetes due to steroid and anti-rejection medications

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

IX. SUMMARY OF NONCLINICAL STUDIES

TransMedics conducted the following nonclinical studies to evaluate the OCS Liver System: (A) engineering bench testing; (B) biocompatibility and biological safety; (C) software verification and validation; (D) cybersecurity; (E) electrical and medical device safety; (F) electromagnetic compatibility; (G) wireless technology; (H) sterilization; (I) shelf life; and (J) animal functional testing.

A. Engineering Bench Testing

TransMedics performed engineering bench testing on the complete OCS Liver System, as well as the Liver Console and the LvPS, to demonstrate that the device meets its product requirements and specifications. In cases when testing was performed on an earlier version of the device, the later design changes did not affect the functions or specifications under evaluation.

B. Biocompatibility and Biological Safety

TransMedics performed a series of biocompatibility studies to demonstrate the safety of the materials of the LvPS. All studies 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 1 below.

Table 1: Summary of the Biocompatibility Testing

Biocompatibility Test	ISO Test Standard	Results
Cytotoxicity Test	10993-5	Non-cytotoxic
Pyrogenicity	10993-11	Non-pyrogenic
Hemocompatibility	10993-4	Non-hemolytic
Sensitization	10993-10	No delayed dermal contact sensitization
Intracutaneous Reactivity	10993-10	No irritation
Acute Systemic Toxicity	10993-11	No systemic toxicity observed
Genotoxicity	10993-3	Non-mutagenic
USP Physicochemical Tests	USP<661> Containers, Plastics	Meets USP limits; no significant extractables

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.

C. Software Verification and Validation

TransMedics performed software verification and validation testing to demonstrate the OCS Liver System performs as intended. The device passed all testing and met its requirements. Software documentation was provided in accordance with the FDA guidance document 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.

D. 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 serial 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.

E. 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 results are shown in Table 2 below.

Table 2: Summary of Electrical, Thermal, and Mechanical Safety Testing

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

F. 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. The results are shown in Table 3 below.

Table 3: Summary of Emission and Immunity Testing

Test	Standard	Results
Radiated Emissions	EN 55011/FCC 47 Part 15C (CISPR 11)	Pass
AC Mains Conducted Emissions	EN 55011/FCC 47 Part 15C (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	RTCA DO 160G	Pass
Radiated Emissions	RTCA DO 160G	Pass
Radiated Emissions	CISPR 25	Pass
Spurious Emissions	FCC 47 CFR Part 15C	Pass

G. 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 are 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."

H. 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.

I. 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 shelf life testing demonstrates the safety and suitability of the LvPS for the labeled shelf life. In addition, real-time and accelerated shelf life testing supports the safety and suitability of the OCS Liver Bile Salts Set for the labeled shelf life.

J. Animal Functional Testing

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

The animal studies used a porcine model to evaluate the performance of the OCS Liver System. TransMedics selected the porcine model because it is a large animal model used in the majority of research for liver perfusion testing and publications. The anatomy and size of a pig liver closely resembles the human liver, making it a clinically suitable animal model that is feasible and practical to use in the laboratory setting.

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

The animal studies performed are summarized in Table 4 below.

Table 4: 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.
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	OCS N=3 vs. Control N=3	OCS arm showed better recovery of function as compared to Cold Control arm.

OCS Liver Preclinical Study	Number of Animals	Summary Results
hours of simulated transplantation		In addition, histology results showed better preserved hepatocellular and hepatobiliary structure 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.

X. SUMMARY OF CLINICAL STUDIES

The primary data set supporting approval of this PMA is the OCS Liver PROTECT trial.

A. Overview of OCS Liver PROTECT Trial Design & Objectives

The OCS Liver PROTECT trial was a prospective, multi-center, randomized trial of 300 patients randomized 1:1 to the OCS Liver or Control (cold storage). The trial enrolled 300 patients at twenty (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 versus 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 $\geq$ 40 years old; or
- Expected total cross clamp/cold ischemic time $\geq$ 6 hours; or
- Donor after Cardiac Death (DCD donor) with age $\leq$ 55 years old; or
- Steatotic liver > 0% and $\leq$ 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. Primary Effectiveness Endpoint

The Primary Effectiveness Endpoint was 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 $\geq$ 10 mg/dL on postoperative day 7;

3) INR $\geq$ 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).

EAD for all patients was adjudicated by the independent Clinical Events Committee (CEC).

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.

3. 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:

1) 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);

2) ischemic biliary complications (ischemic biliary strictures, and non-anastomotic bile duct leaks);

3) vascular complications (liver graft-related coagulopathy, hepatic artery stenosis, hepatic artery thrombosis, and portal vein thrombosis); or

4) liver allograft infections (such as liver abscess, cholangitis, etc.).

4. 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.

5. 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 have 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.

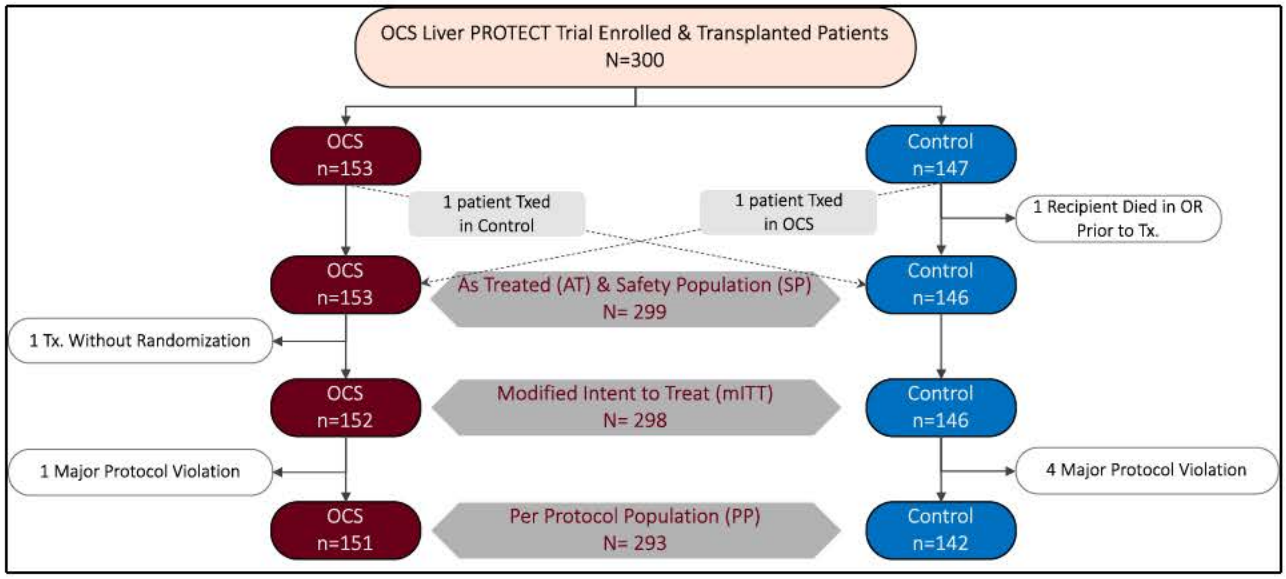
The Modified Intent-to-treat (mITT) population consists of all randomized patients who were transplanted in the trial. In the mITT population, patients were analyzed as randomized. The mITT analyses are the secondary analyses of effectiveness.

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.

B. Trial Enrollment

Three hundred (300) patients were randomized 1:1 to the OCS Liver or Control (cold storage). The enrollment consort diagram is presented in Figure 3 below.

Figure 3: Enrollment Consort Diagram



C. Donor Demographic and Baseline Characteristics

The donor demographics and baseline characteristics are shown in Table 5. The donor organs utilized for this trial were associated with clinical risk factors that may make them more challenging, 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 met more than one donor characteristic. Both donor groups were similar in risk factors of age ≥ 40 years, cross clamp time > 6 hours and macrosteatosis; however, the OCS arm included more DCD and age ≤ 55 years donors (18.4% for OCS vs 8.9% for control). 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 5: Donor Demographic and Baseline Characteristics (AT Population)

Parameter	OCS (N=152[3])	Control (N=146)
Donor Age (years): mean ± SD (Min-Max)	45.84 ± 14.90 (10.9 – 83.7)	46.96 ± 15.22 (13.0 – 80.6)
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%)
• ≥ 40 years old	102 (67.1%)	93 (63.7%)

Parameter	OCS (N=152[3])	Control (N=146)
• 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%)

D. Recipient Demographic and Baseline Characteristics

The recipient demographics and baseline characteristics are shown in Table 6. 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 6: 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	28.4 ± 6.90	28.0 ± 5.71
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%)

Parameter	OCS (N=153)	Control (N=146)
• NASH	24 (15.7%)	20 (13.7%)
• Other	19 (12.4%)	13 (8.9%)

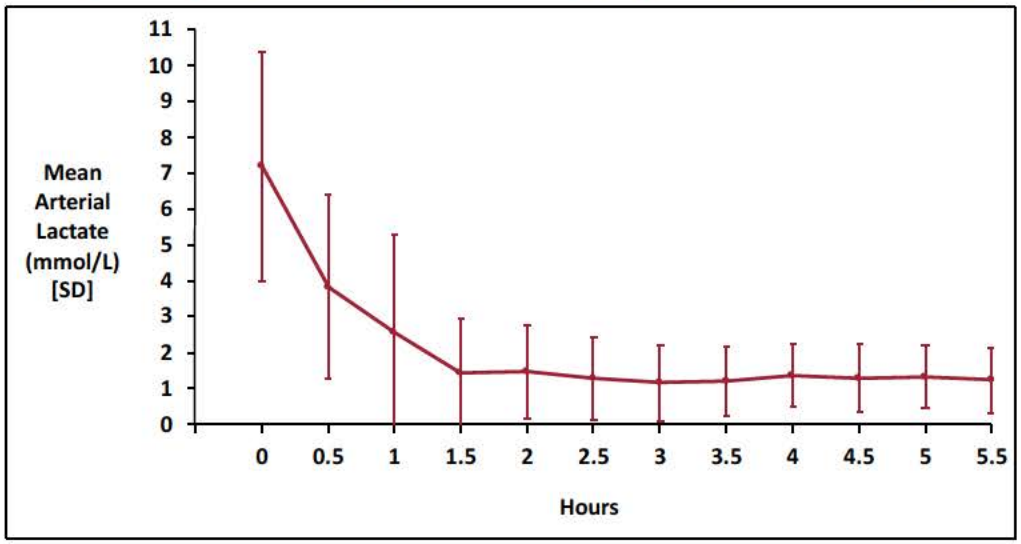
E. OCS Donor Liver Preservation and Assessment

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 7 below). Importantly, the OCS Liver lactate trend showed steady declining and stable trend throughout perfusion indicating that the donor liver has been recovered from the non-physiologic insult of organ donation and procurement to a metabolically active normal liver function. (See **Figure 4**)

Table 7: 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 4: OCS Liver Perfusion Lactate Trend for Transplanted Livers in PROTECT Trial

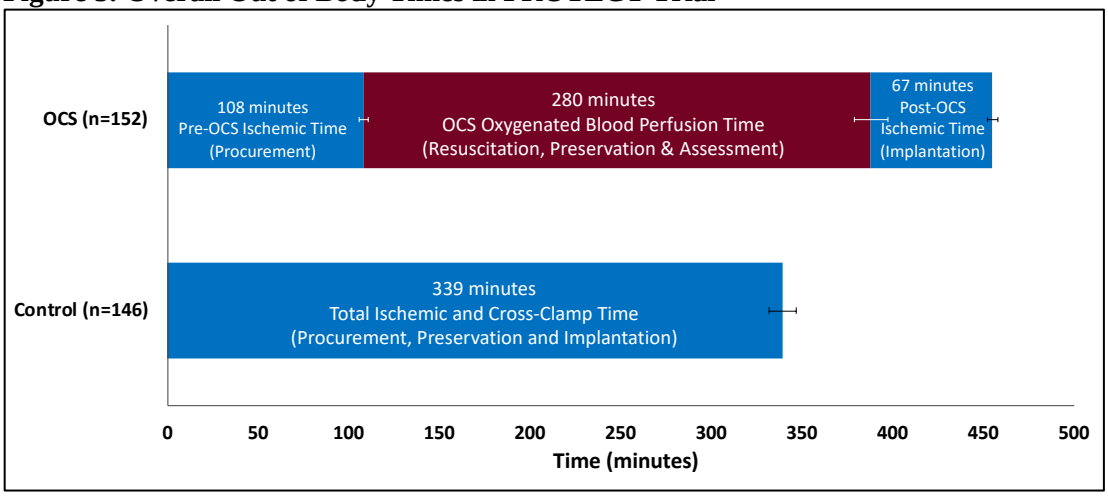


The use of OCS Liver System altered the nature of the critical time from removal from the donor body to reimplantation into the recipient (i.e., total out of body or cross-clamp time). The use of the OCS Liver System significantly reduced the total cold ischemic time on the liver allografts by limiting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

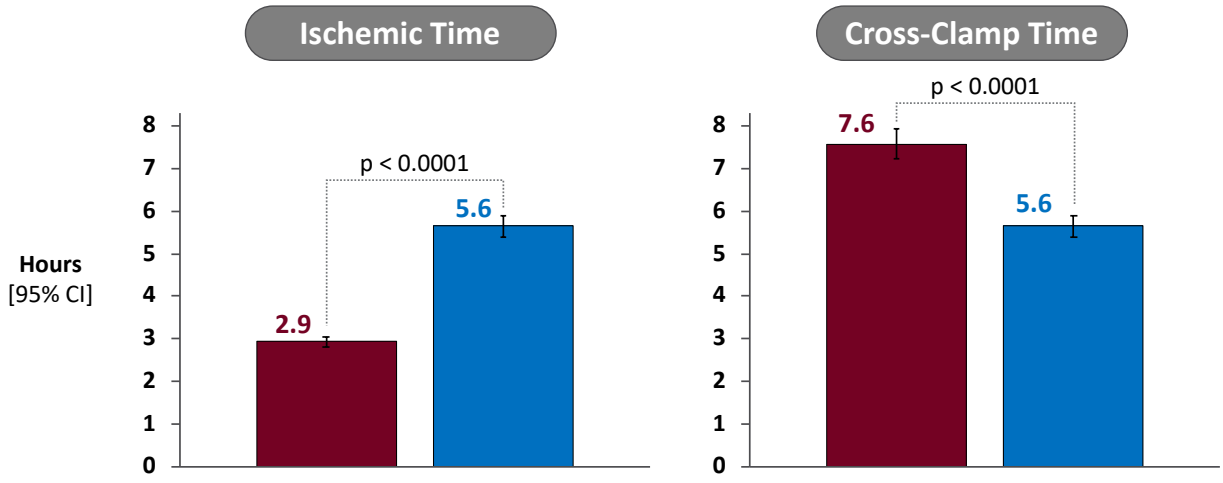
Otherwise, throughout the OCS perfusion, the conditions for the donor liver allograft were not ischemic given that it was perfused on OCS with warm, oxygenated blood perfusate until it was ready to be transplanted. Control liver allografts were ischemic from the time they were procured from the donor body until they were implanted into the recipient. Figure 5 below demonstrates these critical time windows.

Figure 5: 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 6 below).

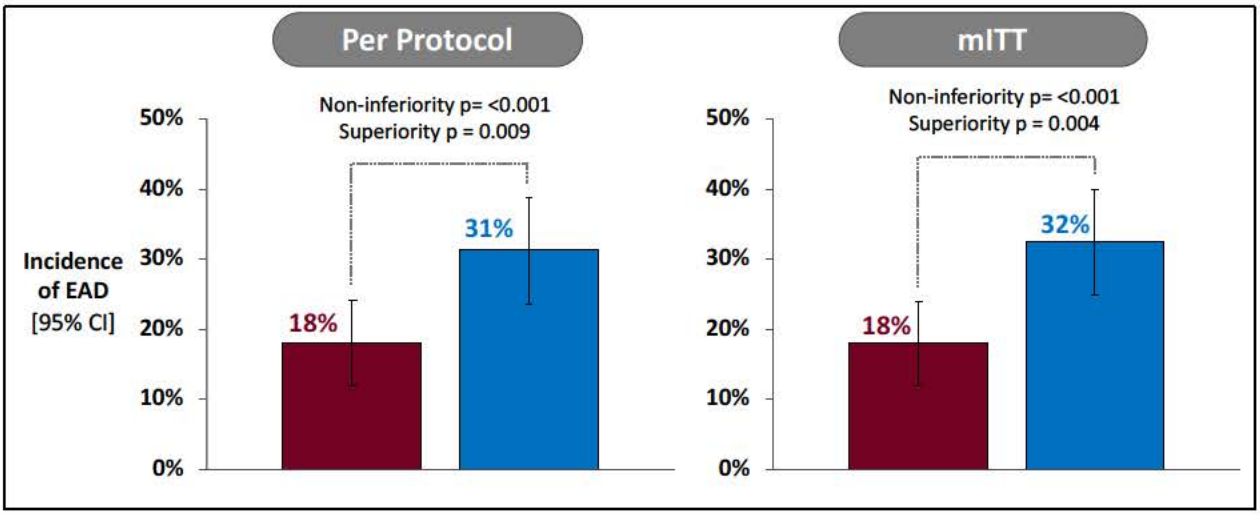
Figure 6: Total Ischemic and Cross-Clamp (Out of Body) Times in PROTECT Trial



F. 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 analysis populations. Specifically, the results demonstrated that use of OCS Liver System was associated with a significant reduction of EAD compared to the Control in the primary analysis PP population (OCS 18.0% vs. Control 31.2%, p=0.009). The same results were experienced in the mITT population (OCS 17.9% vs. 32.4%, p=0.004). See Figure 7 below.

Figure 7: **OCS Liver PROTECT Trial Primary Effectiveness Endpoint - Incidence of Post-Transplant EAD (PP and mITT Populations)**



This significant reduction of EAD associated with the use of OCS Liver System was further validated mechanistically by the histopathological assessment of liver grafts post-transplant. Independent and blind histological assessment revealed significantly less lobular inflammation, a marker of ischemia and reperfusion injury (Ali, et al., 2015; Kakizoe, et al, 1990; Sosa, et al, 2016) (Figure 8 and Figure 9 below).

Figure 8: **Post-Transplant Pathology Assessment – Overall Lobular Inflammation Severity in Biopsy Samples taken 90-120 Minutes Post-reperfusion in Recipient Abdomen (mITT Population)**

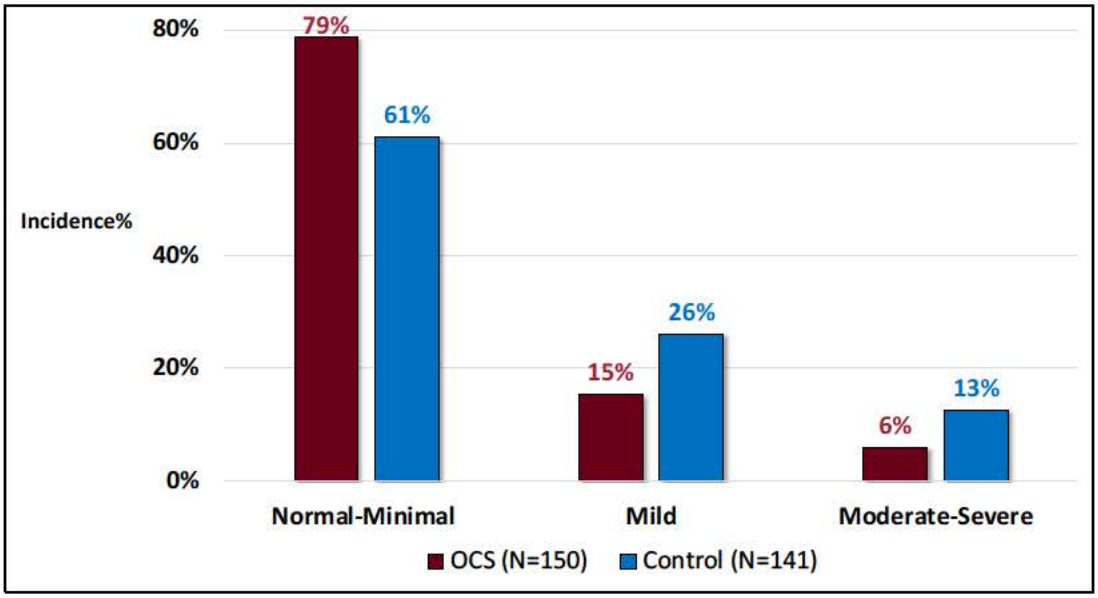
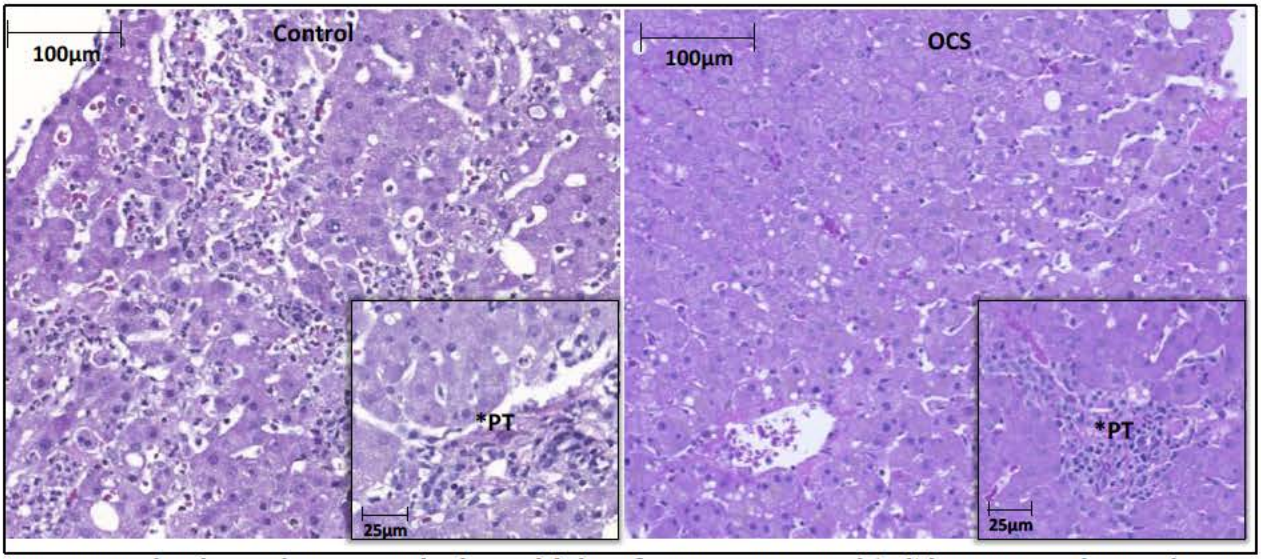


Figure 9: Post-Transplant Histology Representative Sample for Severe Lobular Inflammation from Biopsies Taken 90-120 Minutes Post-reperfusion in Recipient Abdomen



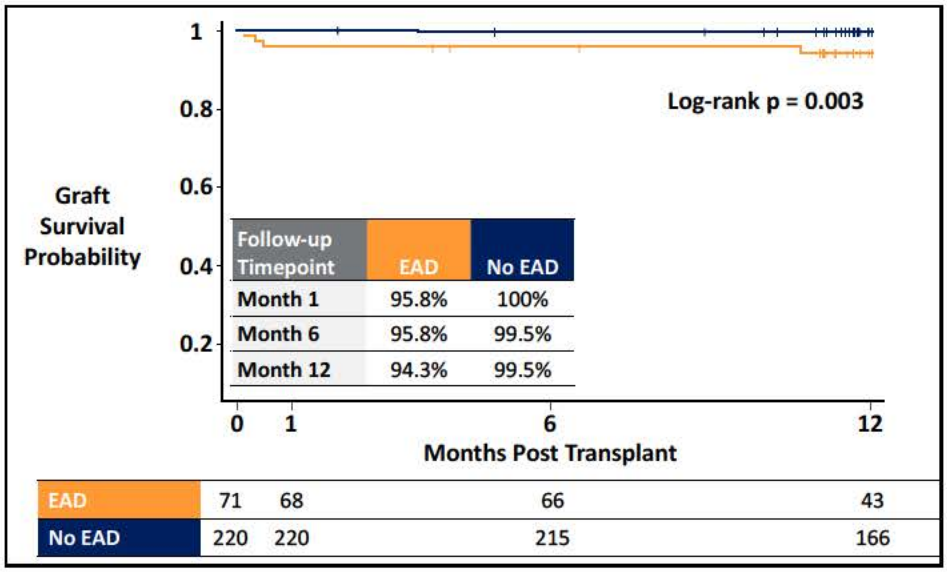
Representative histology to show an example of severe lobular inflammation in a Control (Left) liver post reperfusion with insert showing minimal portal inflammation, and OCS-treated liver (Right) showing absence of lobular inflammation and minimal portal inflammation, insert.

G. Clinical Benefits of Reducing EAD Post-Liver Transplantation

To elucidate the major clinical benefits of reducing EAD post-liver transplantation based on the results of the OCS Liver PROTECT trial, key clinical outcomes of the PROTECT trial were stratified based on the presence or absence of EAD in the overall PROTECT trial population. The results showed that EAD was associated with:

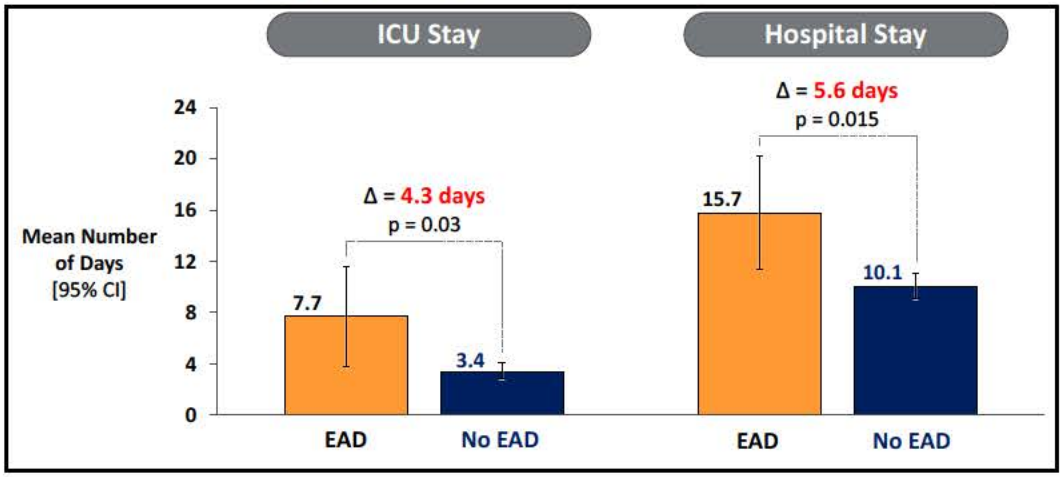
- Significant increased risk for post-transplant graft failure. Graft failure is a serious and devastating clinical outcome for liver transplant recipients. Graft failure would require a re-transplantation or the patient would die (see Figure 10 below).

Figure 10: Kaplan-Meier Liver Graft Survival for PROTECT Subjects (EAD vs. No EAD) (PP Population)



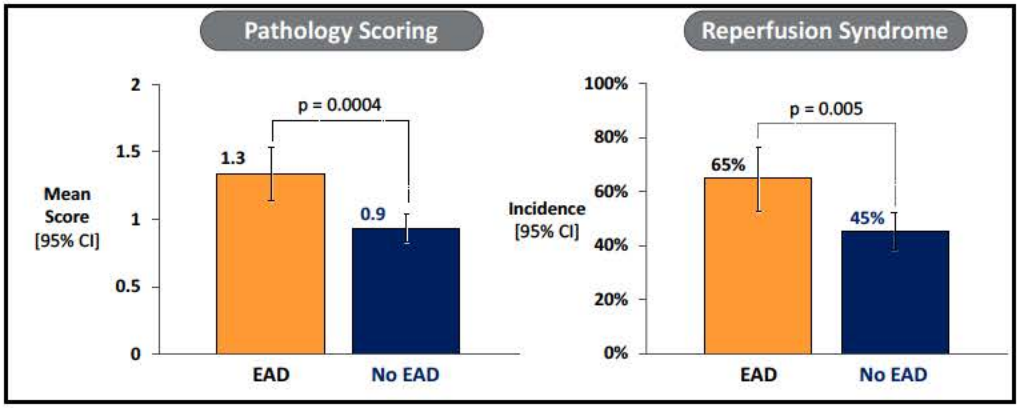
- Significant increase in initial ICU and hospital length of stay post-transplantation. These findings show that the presence of EAD significantly increased hospital resource utilization and ultimately would increase the overall cost for the liver transplant procedure (see Figure 11 below).

Figure 11: 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 IR injury pathological markers) for liver biopsies taken 90-120 minutes post-reperfusion as assessed by independent blinded scoring by the core pathology lab (see Figure 12 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 12 below).

Figure 12: Post-Transplant Overall Pathology Scoring for Biopsies Taken 90-120 Minutes Post-reperfusion (EAD vs. No EAD) (PP Population)



These results demonstrate that the ability of the OCS Liver System's 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.

H. Secondary Effectiveness and OCS Donor Liver Assessment Endpoints

The OCS Liver PROTECT trial met all secondary effectiveness endpoints.

1. OCS Liver System Assessment

The advantage of the OCS 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 all were successfully obtained and measured during preservation.

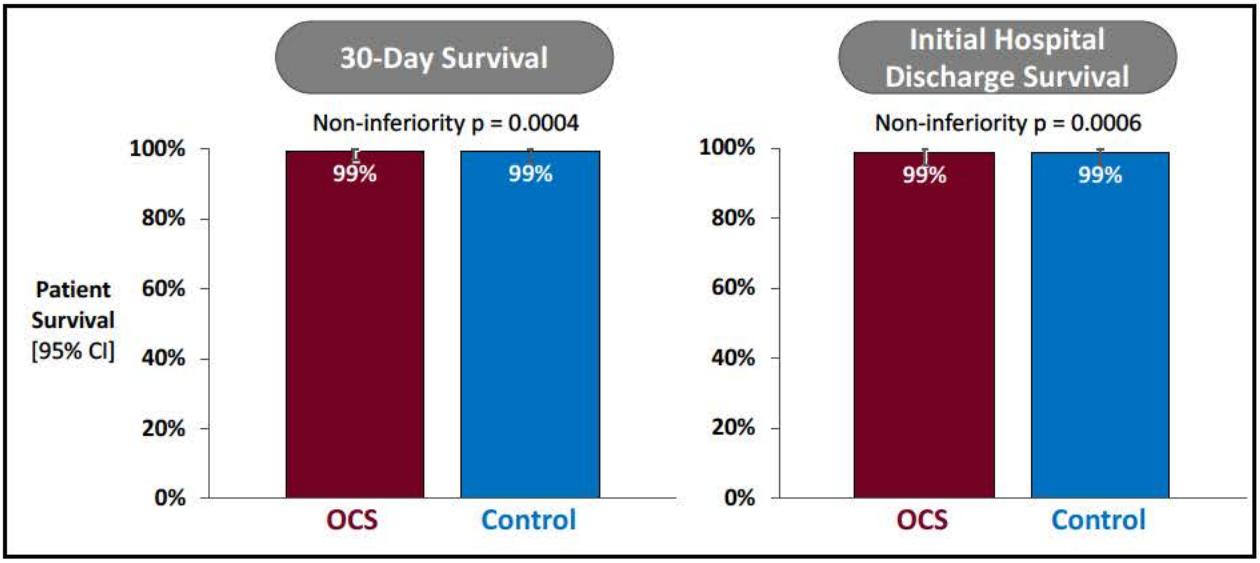
Table 8: First Secondary Endpoint – OCS Liver Assessment Parameters During Perfusion

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 versus the alternative hypothesis that it is greater than 0.85.		

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

The OCS arm 30-day recipients' survival and recipients' survival to initial hospital discharge was high and statistically non-inferior to the Control arm in both the PP and mITT analysis populations. In the PP population, the 30-day survival for both the OCS and Control was 99% and the initial hospital discharge survival was 99% OCS vs 99% Control (see Figure 13).

Figure 13: Second Secondary Effectiveness Endpoint - Recipients' Survival at Day 30 and at Initial Hospital Discharge (PP Population)

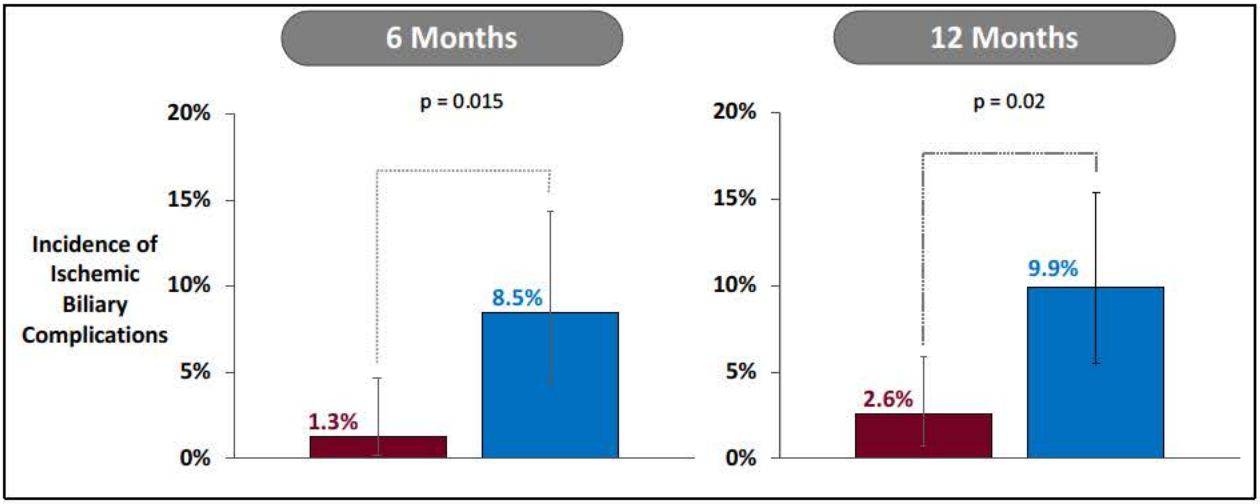


I. Other Clinical Endpoints

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 statistically significantly lower 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 14 below).

Figure 14: Incidence of Ischemic Biliary Complications Through 6 and 12 Months Post-Liver Transplant (PP Populations)



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 ad hoc analysis showing higher recipient mean lactate levels post-reperfusion in the Control group (see Table 9).

Table 9: Assessment of Reperfusion Syndrome – Recipients' Lactate Levels Post-reperfusion in Recipient (mITT Population)

Timepoint	**OCS** Recipient arterial lactate (mmol/L) Mean ± SD	**Control** Recipient arterial lactate (mmol/L) Mean ± SD
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

3. Post-transplant ICU Stay and Initial Hospital Stay

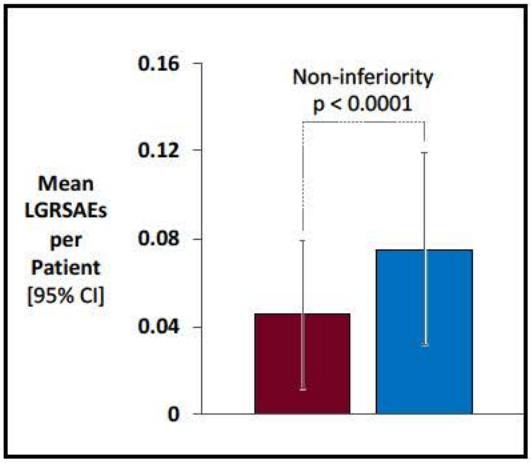
There was no difference in the length of initial post-transplant ICU and hospital stay for the OCS arm compared to the Control arm. The mean ICU stay was 107 hours for OCS compared to 111 hours for Control. The mean hospital stay was 12 days for OCS compared to 11 days for Control.

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 statistically higher incidence of EAD in the Control group compared to the OCS group.

J. 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 15).

Figure 15: 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 10, 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.

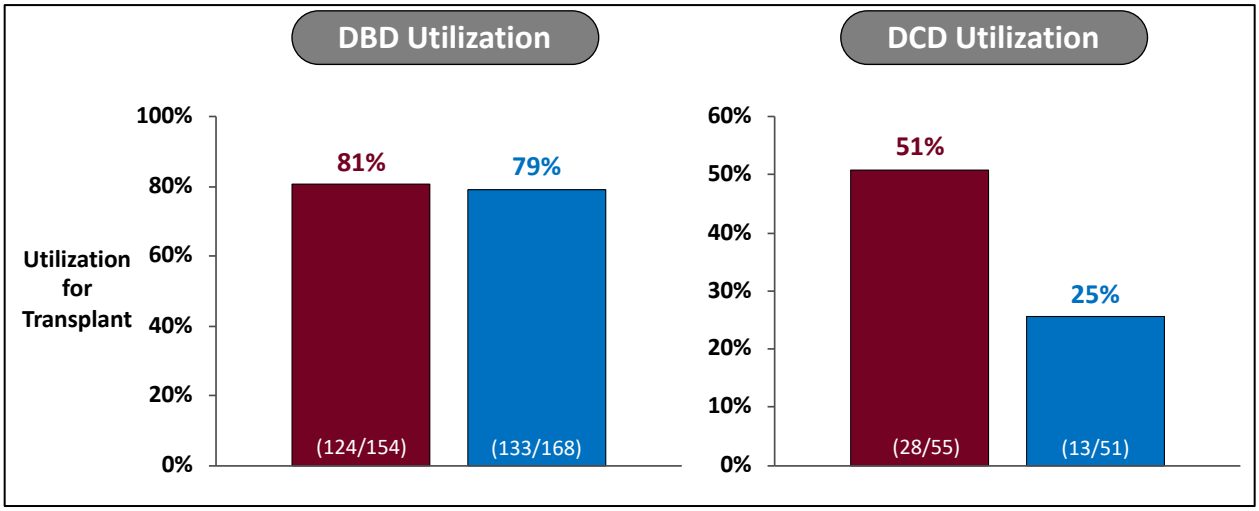
Table 10: LGRSAEs within 30 Days (AT Population)

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

K. Overall Donor Liver Yield from DBD and DCD Donors for Transplantation

The impact of preservation modality on the yield of DBD and DCD livers transplanted in the OCS Liver PROTECT trial was analyzed. There was no difference in yield of transplanted DBD donor livers between using OCS or Control, (OCS 124/154 (80.5%) vs. Control 133/168 (79.2%)); however, there was a substantially higher yield of DCD liver transplants with the use of OCS Liver System compared to Control, (OCS 28/55 (50.9%) vs. Control 13/51 (25.5%)) (see Figure 16 below). These data suggest that the OCS Liver System provided additional opportunity for *ex-vivo* clinical optimization and assessment of the DCD liver graft resulting in doubling the yield of DCD livers transplanted (50.9% vs. 25.5%) compared to the Control arm.

Figure 16: DBD and DCD Donor Liver Utilization Rates in PROTECT Trial

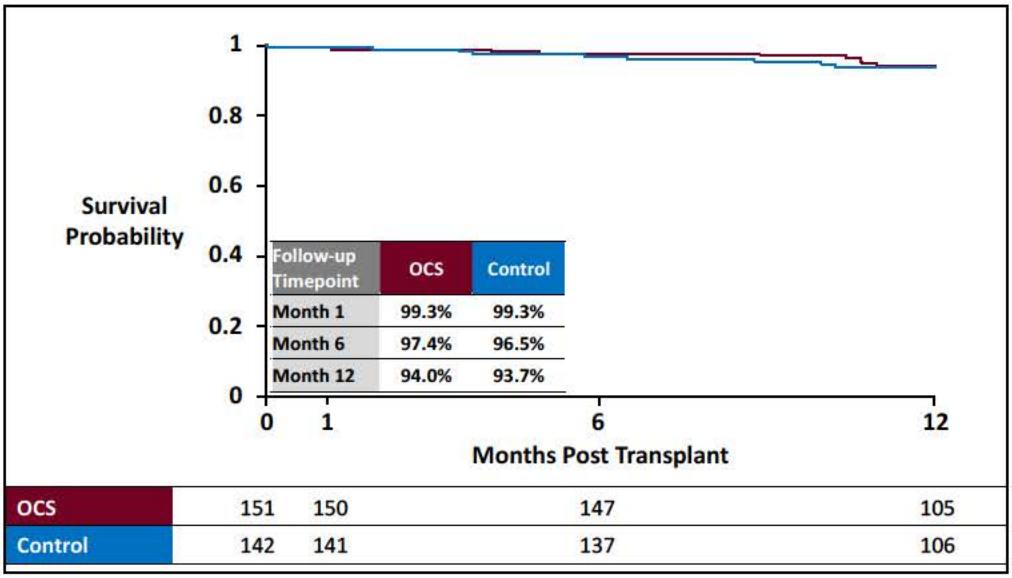


L. Overall Patient Survival Through 12 Months

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 96.6% at 6

months and 94.0% and 93.7% at 12 months for OCS and Control, respectively. (See Figure 17 below).

Figure 17: Kaplan-Meier Overall Patient Survival at Day 30 and through 6- and 12-Month Follow-up Visit (PP Population)



M. Liver Graft Survival

The Kaplan-Meier liver graft survival was similar between OCS and Control. In the PP population, at 6 months post-transplant, liver graft survival was 99% and 99% and at 12 months, liver graft survival was 98.0% and 9% for the OCS and Control groups, respectively.

N. Serious Adverse Events

Serious Adverse Events 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 11 below. As previously discussed, ischemic biliary complications were lower in OCS 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 11: CEC-adjudicated Treatment-Emergent SAEs by Preferred Term (As Treated 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 (SAEs that occurred ≥2% of patients are shown)

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
Anaemia	3 (2.0)	3 (2.0)	1 (0.7)	1 (0.7)
Atrial fibrillation	3 (2.0)	3 (2.0)	4 (2.7)	4 (2.7)

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)
Ascites	1 (0.7)	1 (0.7)	3 (2.1)	3 (2.0)
Pyrexia	2 (1.3)	2 (1.3)	4 (2.7)	4 (2.7)
Biliary ischaemia	4 (2.6)	4 (2.7)	14 (9.6)	14 (9.5)
Hepatic artery stenosis	2 (1.3)	2 (1.3)	4 (2.7)	4 (2.7)
Transplant rejection	5 (3.3)	5 (3.3)	7 (4.8)	8 (5.4)
Wound infection	3 (2.0)	3 (2.0)	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)
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)
Convulsion	2 (1.3)	2 (1.3)	5 (3.4)	5 (3.4)
Delirium	1 (0.7)	1 (0.7)	4 (2.7)	4 (2.7)
Renal failure acute	11 (7.2)	11 (7.3)	7 (4.8)	7 (4.7)
Pleural effusion	1 (0.7)	1 (0.7)	4 (2.7)	4 (2.7)
Respiratory failure	3 (2.0)	3 (2.0)	3 (2.1)	3 (2.0)

O. 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:** 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 pre-retrieval pathology results of widespread bridging fibrosis of the donor liver that was also confirmed by the accepting center's pathologist. This was further verified by an independent core pathology lab examination. 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:** 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, with starting lactate of 10.08 mmol/L and ending lactate of 10.98 mmol/L. The core pathology lab examination revealed significant 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:** 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 while on OCS, with starting lactate of 9.19 mmol/L and ending lactate of 10.25 mmol/L. 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.

P. 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. Donor Characteristics and Demographics

Donor demographics and characteristics are shown in Table 12 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 12: 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%)

Parameter	OCS Patients (N=74)
• Head Trauma (n (%))	12/74 (16.22%)
• 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.	

2. Recipient Demographic and Baseline Characteristics

Recipient demographic and baseline characteristics are shown in Table 13 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 13: 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	

Parameter	OCS Patients (N=74)
• 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%)
o Cholangiocarcinoma	2/74 (2.70%)
o Primary Biliary Cholangitis	1/74 (1.35%)

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 **14** 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 14: 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%)

	OCS Subjects (N=74)
• Primary non-functioning graft within the first 7 days	0/74 (0.00%)

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.

All of the causes of death and liver graft relatedness have been CEC reviewed and adjudicated.

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.

Q. Summary Clinical Conclusions 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 reducing ischemic damage on liver allografts using portable warm, cellular, extracorporeal perfusion on post-transplant clinical outcomes in liver transplantation from DBD and DCD donors.

The OCS Liver PROTECT trial met its primary effectiveness endpoint and demonstrated significant reduction of EAD in both PP and mITT analysis populations compared to the Control arm. EAD is the most common severe complication after liver transplantation and is associated with graft loss, increased ischemia reperfusion injury, and prolonged ICU and hospital stay, which negatively impacts patients' clinical quality of life and healthcare costs 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. In addition, the OCS livers were associated with high and comparable survival at 30 days, at initial hospital discharge, and at 6 and 12 months post-transplant compared to the Control arm. 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.

The use of the OCS Liver System demonstrated a substantial reduction of the most serious post-transplant complication of ischemic biliary complications compared to Control at the 6 and 12 months follow-up timepoints in both the PP and mITT analysis populations. Ischemic biliary complications negatively impact long-term viability of the liver allograft and patient survival.

XI. PEDIATRIC EXTRAPOLATION

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

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

TBD

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The preclinical and clinical data provide ample evidence of effectiveness, safety, and favorable benefit/risk profile to support the OCS Liver System approval for the proposed clinical indication.

A. Preclinical Studies

TransMedics has performed a series of preclinical studies to demonstrate the OCS Liver System meets its performance specifications and that it is safe and effective for the proposed intended use. Preclinical testing included sterilization and shelf life, biocompatibility, software, cybersecurity, electrical safety, EMC, engineering bench testing, and animal functional testing. The testing demonstrates that the OCS Liver System meets its specifications.

B. Clinical Study – PROTECT Trial

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 increased 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 substantially reduced ischemic injury/time on donor livers despite long out of body time. This capability has the potential to 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 demonstrate that the reduction of EAD is associated with:
  - Substantial reduction in risks for post-transplant graft failure;
  - Substantial reduction of post-transplant ICU and hospital length of stay of transplant recipients;
  - Substantial reduction of liver allograft ischemia/reperfusion injury based on histological assessment; and
  - Substantial 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 substantial 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 substantial 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.

C. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on XXXX

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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