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: Organ Care System (OCS™) Liver

Device Procode: QQK

Applicant's Name and Address: TransMedics, Inc.
200 Minuteman Road, Suite 302
Andover, MA 01810

Date of Panel Recommendation: July 14, 2021

Premarket Approval Application (PMA) Number: P200031

Date of FDA Notice of Approval: TBD

II. INDICATIONS FOR USE

The TransMedics® Organ Care System (OCS™) Liver is a portable extracorporeal liver perfusion and monitoring system indicated for preservation and monitoring of hemodynamics and metabolic function which allows for ex vivo assessment of liver allografts from donors after brain death (DBD) or liver allografts from donors after circulatory death (DCD) ≤55 years old and with ≤30 mins of warm ischemic time, macrosteatosis ≤15%, in a near-physiologic, normothermic and functioning state intended for a potential transplant recipient.

III. CONTRAINDICATIONS

The OCS Liver should not be used for:

- Livers with moderate or severe traumatic injury
- Livers with active bleeding (e.g., hematomas)
- Split livers
- Livers with accessory arterial blood supply requiring back table anastomosis.

IV. WARNINGS AND PRECAUTIONS

A device malfunction or user error could lead to loss of a donor organ.
Only trained users should use the OCS Liver System.

Please refer to the TransMedics® Organ Care System OCS Liver User Guide for additional applicable warnings and precautions.

V. DEVICE DESCRIPTION

The **OCS Liver** is an integrated, portable platform designed to maintain donor livers in a near-physiologic, normothermic, and perfused state. The OCS Liver 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 control and monitor the perfusion parameters and bile production. In addition, the perfusion module enables perfusate sampling 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.

These three major components are shown in Figure 1 below.

Figure 1: Components of the OCS Liver

OCS Liver Console	OCS Liver Perfusion Set	OCS Liver Bile Salts
		

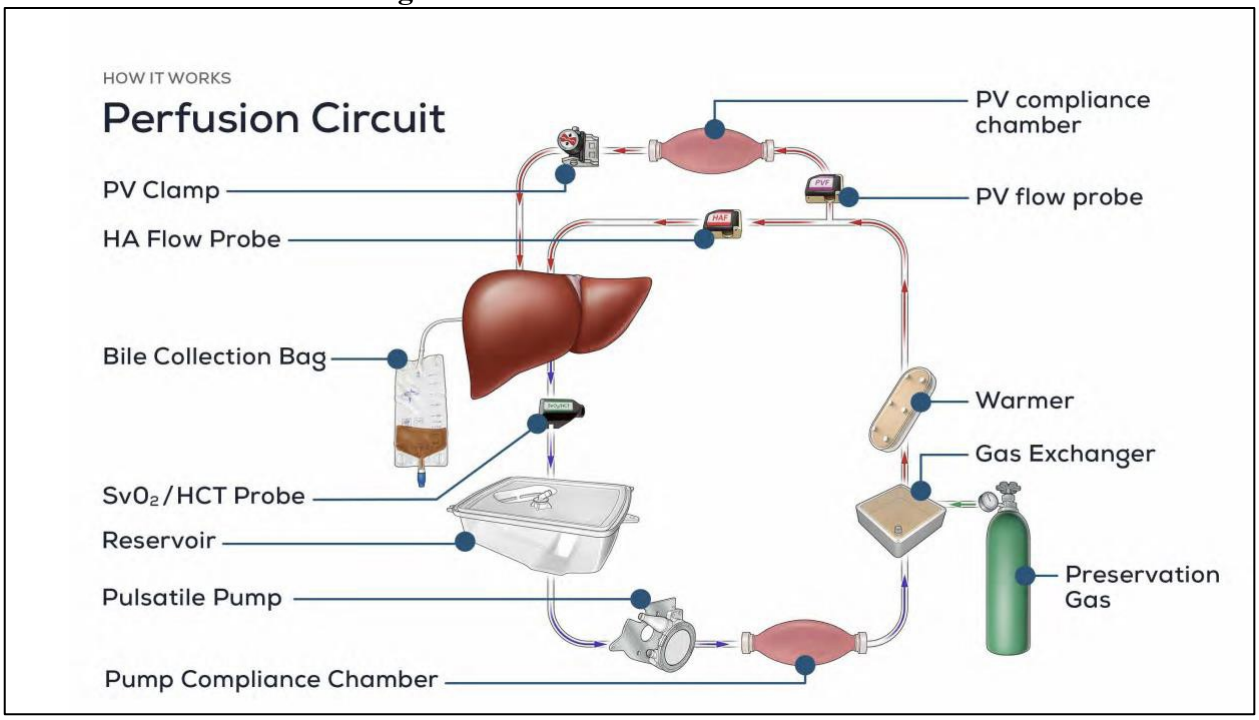
Note: The Liver Console figure (left) shows the LvPM mounted into the system. The LvPS figure (middle) only shows the LvPM.

The OCS Liver preserves the liver in a near-physiological, functioning state by perfusing the liver with a continuously-circulating mixture of warm packed red blood cells (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 (labeled as the gas exchanger). 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 Fluid Flow



To adequately maintain the liver, the OCS Liver 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 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. 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 OCS Liver Console and Liver Perfusion Set (LvPS) have CE mark authorization. However, the OCS Liver has not been commercially distributed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects of the device on health are related to any deleterious effects to subsequent liver transplantation after a harvested donor organ is preserved or attempted to be preserved using the device.

These potential adverse effects include, but are not limited to:

- injury to the donor organ during device instrumentation that
  - will complicate the transplantation surgical procedure;
  - necessitates conversion to an alternative preservation strategy, prolonging ischemic preservation time; or
  - leads to loss of the donor organ; and

- malfunction of the device that
  - leads to physiological conditions (e.g., warm ischemia, or undesirable perfusion parameters) that could adversely affect clinical outcomes of the allograft; or
  - leads to a clinical decision not to proceed with transplantation.

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

- Early liver allograft dysfunction (EAD)
- Acute rejection
- Anastomotic site complications; narrowing, bleeding or occlusion
- Biliary strictures and bile leaks
- Liver primary non-function
- Renal dysfunction and/or failure
- Death
- Bleeding
- Drug Toxicity
- Atrial fibrillation
- Fever
- Delirium, confusion and neurological complications
- Hepatic artery thrombosis
- Pleural effusion
- Convulsion
- Respiratory failure
- Anemia
- Wound Infection
- Ascites
- Aspiration
- Bowel obstruction
- Bowel thromboembolic complications and gangrene
- Cerebrovascular accident
- Cholangitis
- Coagulopathy
- Hemodynamic instability
- Hepatic coma
- Hepatic psychosis
- Hyperacute rejection
- Hyperammonemia
- Ileus
- Liver abscess
- Malignancy
- Multiple organ failure
- Pancreatitis
- Peptic ulceration
- Phrenic nerve injury
- Portal vein thrombosis
- Protamine and other anti-heparin medication reaction
- Sepsis
- Stroke
- Transfusion reaction
- Venous thromboembolism (deep venous thrombosis [DVT])
- Abdominal wound dehiscence
- Diaphragmatic injury
- Gastritis
- Gastro esophageal reflux disease (GERD)
- GI Bleeding (upper or lower)

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: (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, 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 - LvPS

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 on LvPS

Biocompatibility Test	ISO Test Standard	Results
Cytotoxicity Test	10993-5	Non-cytotoxic
Material-Mediated Pyrogenicity	10993-11	Non-pyrogenic
Hemocompatibility (direct/indirect)	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 (complete test battery)	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.

Biocompatibility and Biological Safety – Perfusion Solution

To support the biocompatibility of the recommended perfusion solution, TransMedics conducted the tests in Table 2 below. A Biological risk assessment of Bile Salts/sodium taurocholate was also conducted.

Table 2: Summary of the Biocompatibility Testing for the Perfusion Solution* Mixed with OCS Liver Bile Salts and PlasmaLyte

Biocompatibility Test	ISO Test Standard	Results
Cytotoxicity Test (MEM Elution, with PlasmaLyte)	10993-5	Non-cytotoxic
Hemocompatibility, direct contact** (using PlasmaLyte)	10993-4	Non-hemolytic
Intracutaneous Reactivity (using PlasmaLyte)	10993-10	No irritation
Acute Systemic Toxicity (using PlasmaLyte)	10993-11	No systemic toxicity observed
Pyrogenicity (USP <151> Rabbit Pyrogen, using PlasmaLyte)	10993-11	Non-pyrogenic
Sensitization (Guinea Pig Maximization Sensitization, using PlasmaLyte)	10993-10	No delayed dermal contact sensitization

*The perfusion solution is not sold with the device, but a formulation is included in Section 4.3 of the OCS Liver User Guide.
**Indirect hemocompatibility was not considered applicable, because the test was performed on the bile salt solution that was used as the extract, rather than the typical application of indirect testing intended for materials through which fluids pass before entry into the body.

C. Software Verification and Validation

TransMedics performed software verification and validation testing to demonstrate the OCS Liver 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 Liver does not contain the hardware or software required for many common network interfaces such as USB, Ethernet or Wi-Fi. The OCS Liver incorporates a Wireless Monitor dedicated to the Liver Console. The Wireless Monitor communicates 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 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 3 below.

Table 3: 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 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 met the requirements of the standards. The results are shown in Table 4 below.

Table 4: 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.

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.

ETO and ethylene chlorohydrin (ECH) residuals were evaluated on the entire LvPS, LvPM, LvPS accessories and the bile salts together 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.

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 12-month 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 three-year shelf life.

J. Animal Functional Testing

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

The animal studies used a porcine model to evaluate the performance of the OCS Liver. 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 to meet the performance specifications and that the configuration of the OCS Liver worked successfully during simulated surgical procedures. The animal studies performed are summarized in Table 5 below.

Table 5: Summary of Animal Functional Studies

OCS Liver Preclinical Study	Number of Animals	Summary Results
Phase 1: Up to 12-hour preservation on OCS Liver	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 versus 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 versus Control N=3	OCS arm showed better recovery of function as compared to Cold Control arm. In addition, histology results showed better preserved hepatocellular and hepatobility 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 met all the acceptance criteria for this validation.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of liver transplant with the OCS Liver in the US under IDE #G140192. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between January 24, 2016 and October 15, 2019. The database for this PMA reflected data collected through October 15, 2020 and included 429 consented recipients. There were 20 investigational sites.

The OCS Liver PROTECT trial was a prospective, multi-center, unblinded, randomized trial comparing the OCS Liver to Control (cold storage). The clinical objective of the trial was to compare the safety and the effectiveness of the OCS Liver 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 ≥ 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)).

A clinical events committee, comprised of three experienced experts in the field (two liver transplant surgeons and one liver transplant hepatologist), reviewed trial events. A Data Safety Monitoring Board, comprised of a liver transplant surgeon, liver transplant hepatologist, and an independent biostatistician, monitored the trial.

The control group was transplantation with the current standard of care, cold static storage.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the PROTECT study was limited to donor livers and recipients who met the following inclusion criteria.

   Donor Liver Eligibility Criteria:

   Inclusion Criteria - donors were required to meet at least one of the following:
   - 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)).

   Donor Livers were not permitted to enroll in the PROTECT study if they met any of the following exclusion criteria:

   Exclusion Criteria - donor livers were excluded if they met any of the following

criteria:

- Living donors
- Liver intended for split transplants
- Positive serology (HIV, Hepatitis B surface antigen and C)
- Presence of moderate or severe traumatic liver injury, or anatomical liver abnormalities that would compromise ex-vivo perfusion 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 Eligibility Criteria:

Inclusion Criteria

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

Transplant recipient were not permitted to enroll in the PROTECT study if they met any of the following exclusion criteria:

Exclusion Criteria:
Recipients were excluded if they meet 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 inotrope to maintain hemodynamics

2. Follow-up Schedule
All patients were scheduled to return for follow-up examinations at day 0, day 7, hospital discharge, day 30, 6 months, 12 months, and 24 months after transplant was received.

Pre- and post-implant assessments included medical history, Early Liver Allograft Dysfunction surveillance, mechanical ventilator support, liver graft-related adverse events, ICU or hospital stay, liver graft-related adverse events and serious adverse events, patient/graft survival and in some cases liver biopsy.

The detailed post-transplant assessment and follow-up schedules are shown in

Table 6.

Table 6: Recipient Schedule of Assessments

Evaluations	Recipient Schedule of Assessments					
	Tx. Day --- Day 7 Post-Tx.	**Discharge**	**Day 30**	**Month 6**	**Month 12**	**Month 24**
Eligibility & Informed Consent	X					
Randomization	X					
Demographic/Characteristics	X					
Medical & Risk Factors	X					
Transplant Details	X					
Early Liver Allograft Dysfunction Surveillance	X					
Mechanical Ventilator Support	X					
Patient Survival	X		X	X	X	X
Graft Survival	X		X	X	X	X
Immunosuppressive Meds & Induction (if applicable)	X	X				
Initial ICU & Hospital Stay	X	X				
Liver Graft-Related AE's & SAE's	X	X	X			
Liver Biopsy *	X				X	X

*only tests regularly scheduled per center SOC or performed due to a clinical cause will be collected.

3. Clinical Endpoints

The safety endpoint is the average number of liver graft-related serious adverse events (LGSAEs) 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.).

The PROTECT trial included the following Effectiveness endpoints:

The Primary Effectiveness Endpoint was the incidence of Early 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).

The primary effectiveness endpoint of EAD is loosely based on the 2010 Olthoff[l] publication, which attempted to validate this surrogate endpoint in liver transplant recipients. The Agency notes that the Olthoff definition includes the assessment of ALT in addition to AST, INR, and bilirubin. In the EAD definition used in the PROTECT Trial, ALT is left out and ALT levels within the first 7 days following transplantation are not included in the calculation of whether the recipients met the definition of EAD.

Secondary Effectiveness and OCS Donor Liver Assessment Endpoints include:

- OCS Donor Liver Assessment Endpoint, defined as successful measurement of donor liver perfusion parameters during preservation, including:
  - Lactate levels
  - Hepatic Artery and Portal Vein Pressure
  - Average Bile Production Rate
- Patient survival at day 30 post-transplantation
- Patient survival at initial hospital discharge post liver transplantation.

Other Clinical Endpoints include:
- 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.

Regarding success/failure criteria, the primary hypothesis for this trial was that the OCS treatment is non-inferior to the Control with respect to EAD. The statistical null and alternative hypotheses for the primary effectiveness endpoint are:

$$H_{10}: \pi_{1,OCS} \geq \pi_{1,Control} + \delta,$$
$$H_{11}: \pi_{1,OCS} < \pi_{1,Control} + \delta,$$

where $\pi_{1,OCS}$ and $\pi_{1,Control}$ are the true proportions of recipients with EAD within the first 7 postoperative days for the OCS and Control, respectively, and δ is the noninferiority margin 0.075. The hypothesis was planned to be evaluated using the Farrington and Manning score statistic with one-sided alpha of 0.05.

If non-inferiority is demonstrated, the results were to be tested for superiority, using Fisher's exact test with a two-sided alpha of 0.05.

B. Accountability of PMA Cohort

At the time of database lock, of 429 patients enrolled in the PMA study, 41% of patients were available for analysis at the completion of the study, the 24-month post-operative visit.

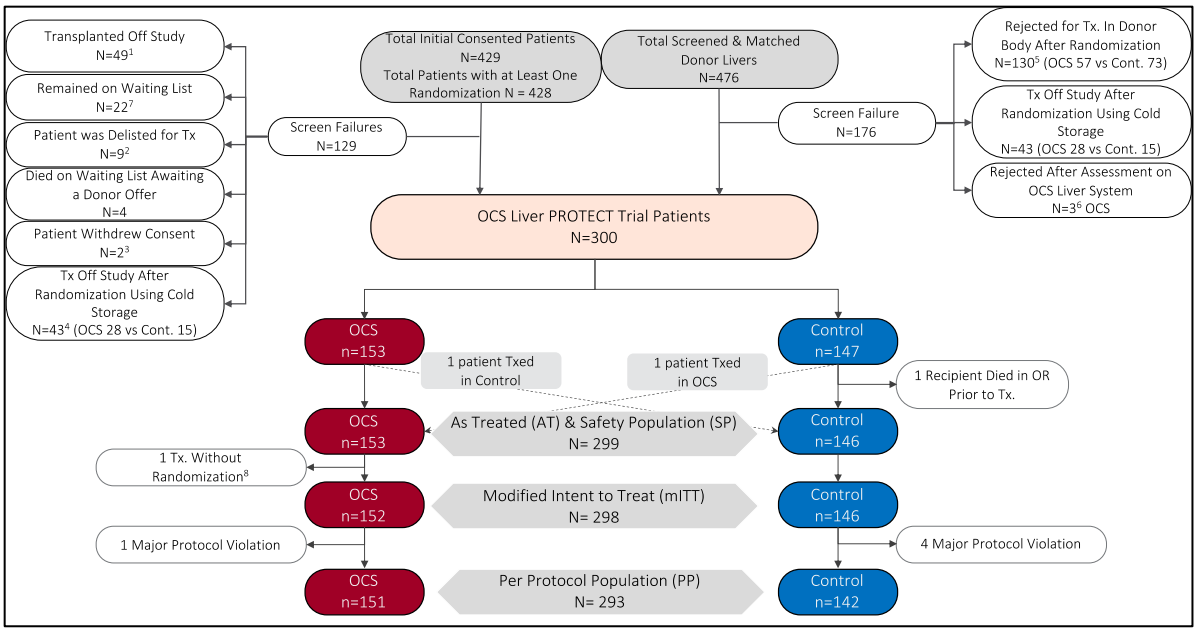
A total of 429 patients signed informed consent and 428 received one or more randomizations in the PROTECT trial. For the randomized patients, there were 476 matched donors that had an initial screening, and 300 were considered to be in the PROTECT trial (OCS 153 and Control 147). The enrollment consort diagram is presented in Figure 3 below.

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 (also called the Safety Population (SP)) 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 Intent-to-Treat (ITT) population consists of the mITT population defined above plus an additional N=43 randomized subjects who were transplanted off-study using cold storage with a matched organ, plus two other randomized subjects for whom the preservation method was initiated but who did not receive a transplant due to death or donor liver turn down.

Figure 3: Enrollment Consort Diagram



[1] Patient withdrawn and transplanted (Tx) Off Study with a Non-Study- Liver Preserved Using Cold storage after Initial Donor Offer(s) were Declined for Tx at Retrieval and initial randomization(s) were broken (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] Patient withdrawn and transplanted Off Study with a Liver matched at randomization but Preserved 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 Transplant-by-Transplant Surgeon after clinical interpretation of Ex vivo Assessment Data obtained during OCS perfusion N=3

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

[7]Patient remained on waiting list at the end of study N=22 – includes 1 patient who had a donor liver turndown after OCS Liver Preservation and Assessment

[8]One patient was transplanted on OCS with a Non-randomized liver. This patient is included in the AT population but not in the mITT or PP populations.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a liver transplant study performed in the US.

The donor demographics and baseline characteristics are shown in Table 7 and Table 8. 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 donors (18% for OCS versus 9% for control).

Table 7: 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, n (%)		
• 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], n(%)		
• ≥ 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 LV-01-999, as this patient was not randomized.

Table 8: Additional Donor Characteristics for DBD and DCD Livers in PROTECT Trial (AT Population)

Parameter	DBD		DCD	
	OCS	Control	OCS	Control
Donor Age (years)				
Mean	47.9	47.9	36.8	37.6
Median	51.0	47.5	37.8	36.7
Min-Max	10.9-83.7	13.0-80.6	15.2-54.0	23.3-51.5
Macrosteatosis (%)				
Mean	4.5	3.1	0.9	6.8
Median	0.0	0.0	0.0	0.0
Min-Max	0.0-30.0	0.0-25.0	0.0-15.0	0.0-40.0
Cold Ischemic Time (min)				
Mean	174.7	338.6	178.3	341.1
Median	165.5	331.0	168.5	350.0
Min-Max	115.0-420.0	154.0-660.0	115.0-273.0	175.0-479.0
Warm Ischemic Time (min)				
Mean			21.0	21.7
Median			22	21
Min-Max			7-31	14-33
Weight (kg)				
Mean	87.7	86.4	85.9	90.5
Median	88.3	82.5	78.5	85.8
Min-Max	48.0-153.2	46.5-183.0	56.0-134.0	67.3-139.6

The recipient demographics and baseline characteristics are shown in Table 9. 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 9: 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, n (%)		
• 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, n (%)	44 (28.8%)	44 (30.1%)
History of liver cancer, n (%)	60 (39.2%)	63 (43.2%)
Primary diagnosis, n (%)		
• 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%)

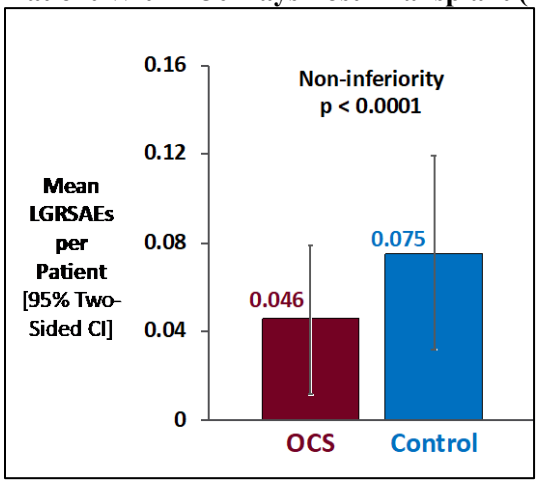
D. Safety and Effectiveness Results

1. Safety Results

Safety Endpoint, LGRSAEs

There was a pre-specified safety endpoint based on the number of liver graft-related serious adverse events (LGRSAEs) in the cohort of 299 recipients available for the 30-day evaluation. LGRSAE results are presented in Figure 4 and Table 10 below.

Figure 4: Safety Endpoint – Average number of LGRSAEs Per Transplanted Patient Within 30 Days Post-Transplant (AT Population)



The specific LGRSAEs are shown in Table 10. The OCS patients did not experience any ischemic biliary complications in the first 30 days post-transplant, while 2/146 (1%) of control patients had ischemic complications. Vascular complications occurred in 7/153 (5%) of OCS patients compared to 9/146 (6%) of control patients. There were no incidents of non-functioning graft or liver allograft infection for either OCS or control patients.

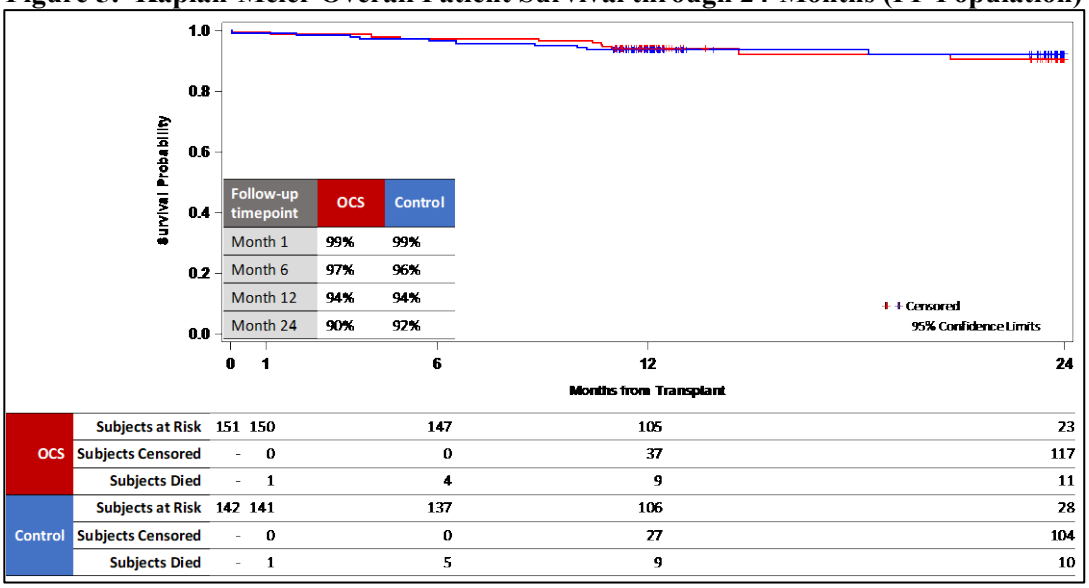
Table 10: LGRSAEs within 30 Days (AT Population)

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

Patient Survival

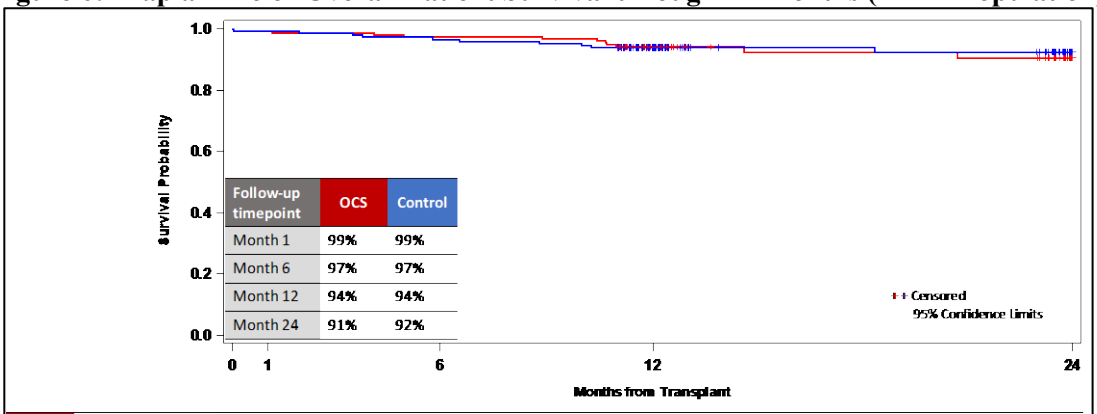
Despite the lower rate of EAD for OCS compared to control, there was no difference in patient or graft survival for the OCS arm compared to the Control arm. Overall patient survival was high and comparable between the OCS and Control arms. The 30-day patient survival for both arms is 99.3%. The patient survival is 97.4% and 96.5% at 6 months and 94.0% and 93.7% at 12 months for OCS and Control, respectively in the PP population. These results are shown in Figure 5 below. Survival for the mITT population is similar, as are the results for the ITT population analysis (Figure 6 and Figure 7).

Figure 5: Kaplan-Meier Overall Patient Survival through 24-Months (PP Population)



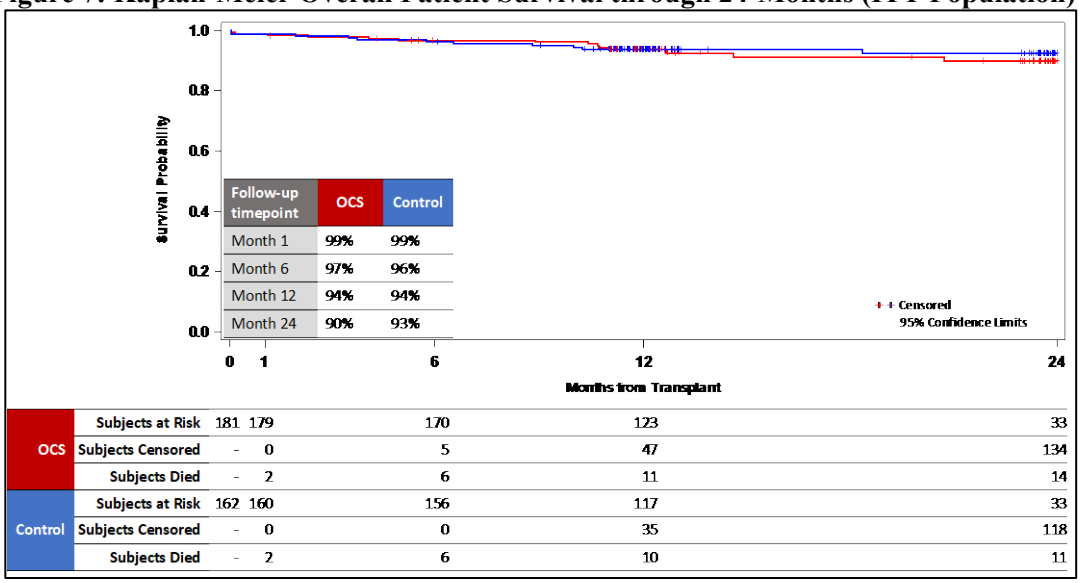
OCS	Subjects at Risk	151	150	147	105	23
	Subjects Censored	-	0	0	37	117
	Subjects Died	-	1	4	9	11
Control	Subjects at Risk	142	141	137	106	28
	Subjects Censored	-	0	0	27	104
	Subjects Died	-	1	5	9	10

Figure 6: Kaplan-Meier Overall Patient Survival through 24-Months (mITT Population)



OCS	Subjects at Risk	152	151	148	105	23
	Subjects Censored	-	0	0	38	118
	Subjects Died	-	1	4	9	11
Control	Subjects at Risk	146	145	141	110	30
	Subjects Censored	-	0	0	27	106
	Subjects Died	-	1	5	9	10

Figure 7: Kaplan-Meier Overall Patient Survival through 24-Months (ITT Population)*



OCS	Subjects at Risk	181	179	170	123	33
	Subjects Censored	-	0	5	47	134
	Subjects Died	-	2	6	11	14
Control	Subjects at Risk	162	160	156	117	33
	Subjects Censored	-	0	0	35	118
	Subjects Died	-	2	6	10	11

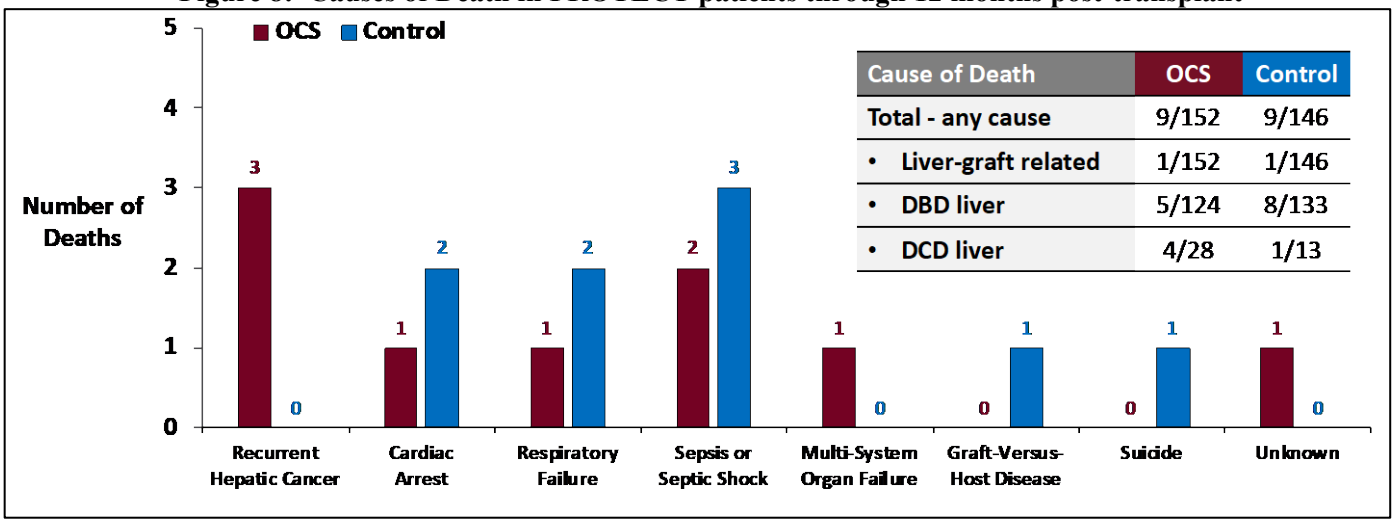
*Note that at 24 months, 3 deaths in OCS group occurred in subjects transplanted off-study using cold-storage

Post-transplant ICU Stay and Initial Hospital Stay

The mean ICU stay was 107± 201.6 hours for OCS compared to 111 ± 260.3 hours for Control. The mean hospital stay was 11.7 ± 11.4 days for OCS compared to 11.4 ± 12.7 days for Control. The results are highly variable for both groups with wide confidence intervals.

The causes of death for PROTECT patients are shown in Figure 8 below.

Figure 8: Causes of Death in PROTECT patients through 12 months post-transplant



Cause of Death	OCS	Control
Total - any cause	9/152	9/146
• Liver-graft related	1/152	1/146
• DBD liver	5/124	8/133
• DCD liver	4/28	1/13

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 these events is shown in Table 11 below. As previously discussed, ischemic biliary complications were lower in OCS compared to the Control group. Non-ischemic biliary anastomotic complications were higher in the OCS arm; however, bile leaks were higher in the Control arm. 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 in ≥2% of patients in either arm 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
Biliary ischaemia	4 (2.6)	4 (2.7)	14 (9.6)	14 (9.5)
Biliary anastomosis complication	13 (8.5)	13 (8.7)	6 (4.1)	6 (4.1)
Post procedural bile leak	4 (2.6)	4 (2.7)	11 (7.5)	11 (7.4)
Renal failure acute	11 (7.2)	11 (7.3)	7 (4.8)	7 (4.7)
Transplant rejection	5 (3.3)	5 (3.3)	7 (4.8)	8 (5.4)
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)
Drug toxicity	5 (3.3)	5 (3.3)	2 (1.4)	2 (1.4)
Atrial fibrillation	3 (2.0)	3 (2.0)	4 (2.7)	4 (2.7)
Pyrexia	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)
Hepatic artery stenosis	2 (1.3)	2 (1.3)	4 (2.7)	4 (2.7)
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)
Ascites	1 (0.7)	1 (0.7)	3 (2.1)	3 (2.0)
Wound infection	3 (2.0)	3 (2.0)	0	0
Anaemia	3 (2.0)	3 (2.0)	1 (0.7)	1 (0.7)

Device Malfunctions

In the OCS Liver PROTECT trial, there were three device malfunctions reported by trial centers (3/155, 1.9%). Two of three 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 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. 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. The user flushed the portal vein directly through the PV cannula and bypassed the defective valve.

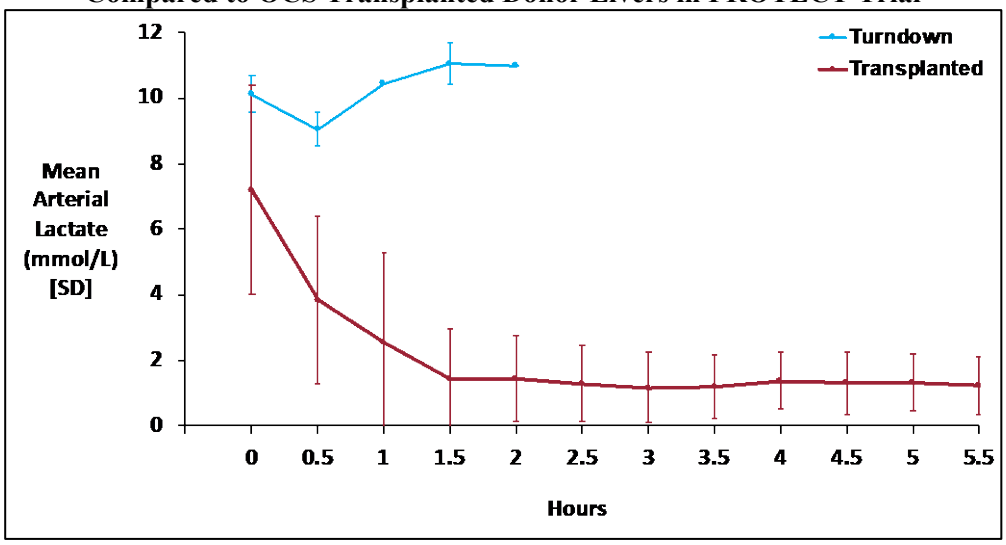
- One malfunction occurred during pre-retrieval OCS preparation, when the OCS liver perfusion module electrical connection could not be recognized by the OCS Liver Console. This occurred well before the liver was surgically retrieved. The retrieval and preservation proceeded using cold static storage without any issues.

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

Donor Liver Clinical Turndown After Assessment on OCS Liver

There were three DCD donor livers that were clinically turned down for transplantation. Two cases were due to rising lactate while being perfused on OCS Liver and one case was due to pre-retrieval pathology results. Figure 9 shows how the lactate levels, obtained during donor liver perfusion on the OCS Liver, in these three turndown livers compared to other livers in the OCS arm. No organs were turned down in the cold storage Control arm. The donor organ turndown impacted one recipient in the PROTECT trial who underwent unnecessary anesthesia prior to the donor organ turndown. No potential recipients underwent unnecessary incision.

Figure 9: Mean OCS Liver Arterial Lactate Trend for Turned Down Donor Livers Compared to OCS Transplanted Donor Livers in PROTECT Trial

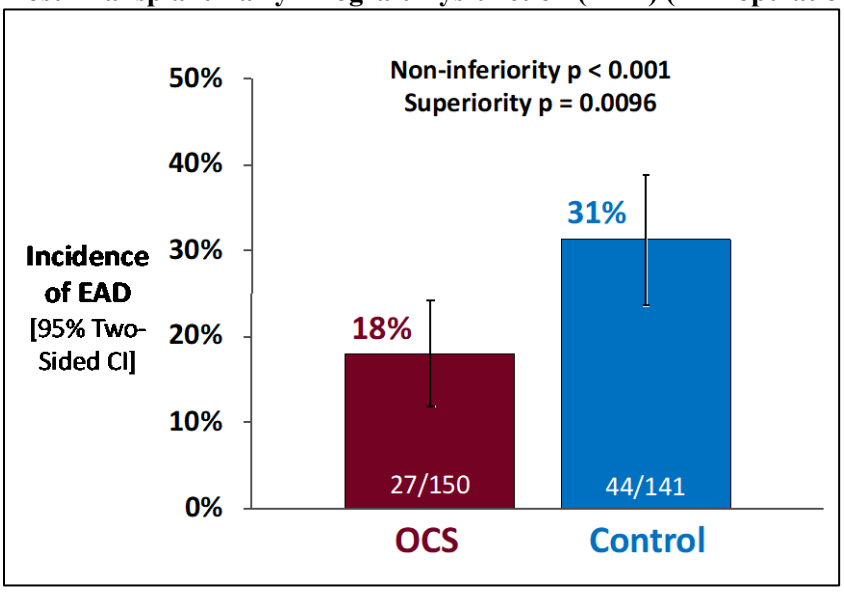


2. Effectiveness Results

Primary Effectiveness Results

The primary endpoint for effectiveness was based on the 291 evaluable patients at the 7-day time point. The OCS Liver PROTECT trial met its primary effectiveness endpoint regarding Early Allograph Dysfunction (EAD) by demonstrating statistical non-inferiority (NI margin=7.5%, $p<0.001$) and superiority of outcomes of the OCS arm compared to Control. The results demonstrated that use of OCS Liver was associated with a significant reduction of EAD compared to the Control in the primary analysis PP Population (OCS 18% (27/150) versus Control 31% (44/141) superiority $p=0.009$). See Figure 10 below.

Figure 10: OCS Liver PROTECT Trial Primary Effectiveness Endpoint - Incidence of Post-Transplant Early Allograft Dysfunction (EAD) (PP Population)



Since the primary effectiveness endpoint EAD is a composite endpoint, each of the individual components of EAD (AST, bilirubin, and INR) were evaluated separately to see whether EAD incidence is driven by one component, and to ensure the similar trending across each component. Table 11 shows the number of recipients who met each of the seven possible combinations of the three EAD components.

In the PROTECT trial, most EAD events are driven by AST only, which is shown in row 3 (17 in OCS and 36 in Control) in Table 12 below.

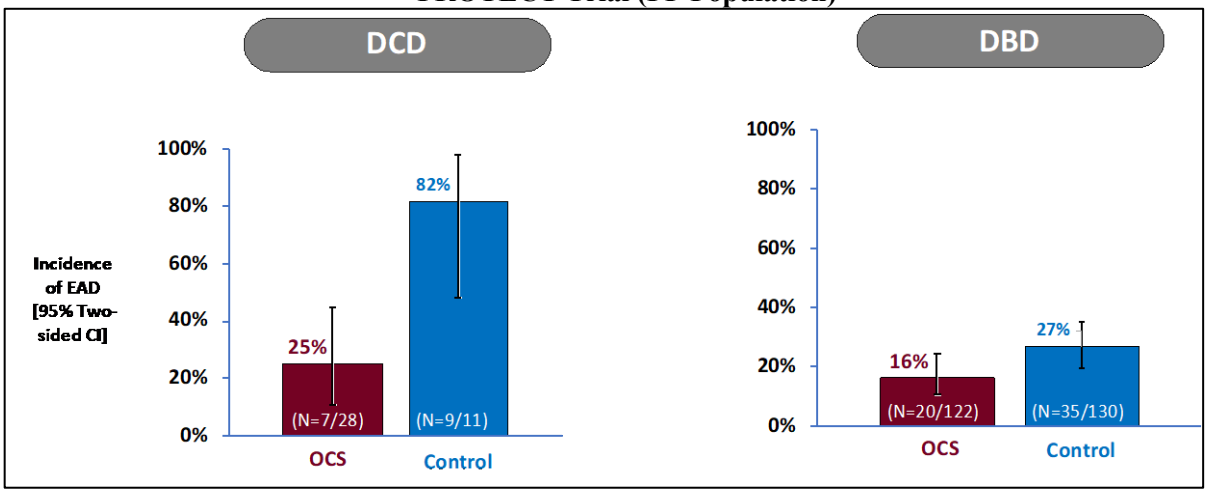
Table 12: Frequency Table for 7 Different Combinations of Individual Components of the EAD Definition (296 Recipients: 151 OCS and 145 Control)

Row	Components of EAD			Number of Recipients	
	INR≥1.6 at Day 7	Bilirubin≥10 at Day 7	AST>2000 during Wk1		
				OCS N	Control N
1	INR≥1.6	-	-	3	2
2	-	Bilirubin≥10	-	4	2
3	-	-	AST>2000	17	36
4	INR≥1.6	Bilirubin≥10	-	0	0
5	-	Bilirubin≥10	AST>2000	0	3
6	INR≥1.6	Bilirubin≥10	AST>2000	2	2
7	INR≥1.6	-	AST>2000	1	2
Total				27	47

Generated by the FDA reviewer
Source: the sponsor's submitted dataset "ADSL" in the amendment

A reduction in EAD was experienced in both the DBD and DCD donor cohorts in the PROTECT trial (Figure 11).

Figure 11: Incidence of Post-Transplant EAD in DBD and DCD Donor Cohorts in PROTECT Trial (PP Population)



Secondary Effectiveness Endpoint, OCS Donor Liver Assessment During Perfusion

The OCS Liver allows for continuous monitoring of the donor liver during preservation. The rates of successful measurement of lactate levels, bile production, hepatic artery pressure, and portal vein pressure are shown in Table 13.

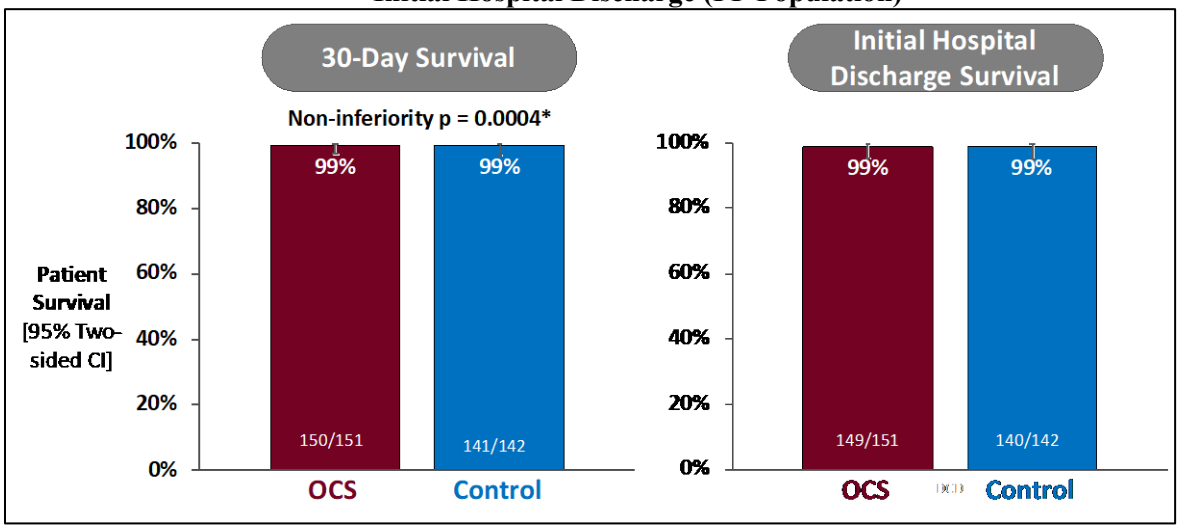
Table 13: Secondary Endpoint – OCS Liver Assessment Parameters During Perfusion

OCS Liver Perfusion Parameters	
Percentage of livers for which OCS device monitoring allowed for ex vivo assessment prior to transplant	**93% (144/155)**
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.	

Recipient Survival at Day 30 and at initial hospital discharge

The 30-day recipient survival and recipient survival to initial hospital discharge were high and similar in the OCS and Control arms (Figure 12).

Figure 12: Secondary Effectiveness Endpoints - Recipients' Survival at Day 30 and at Initial Hospital Discharge (PP Population)



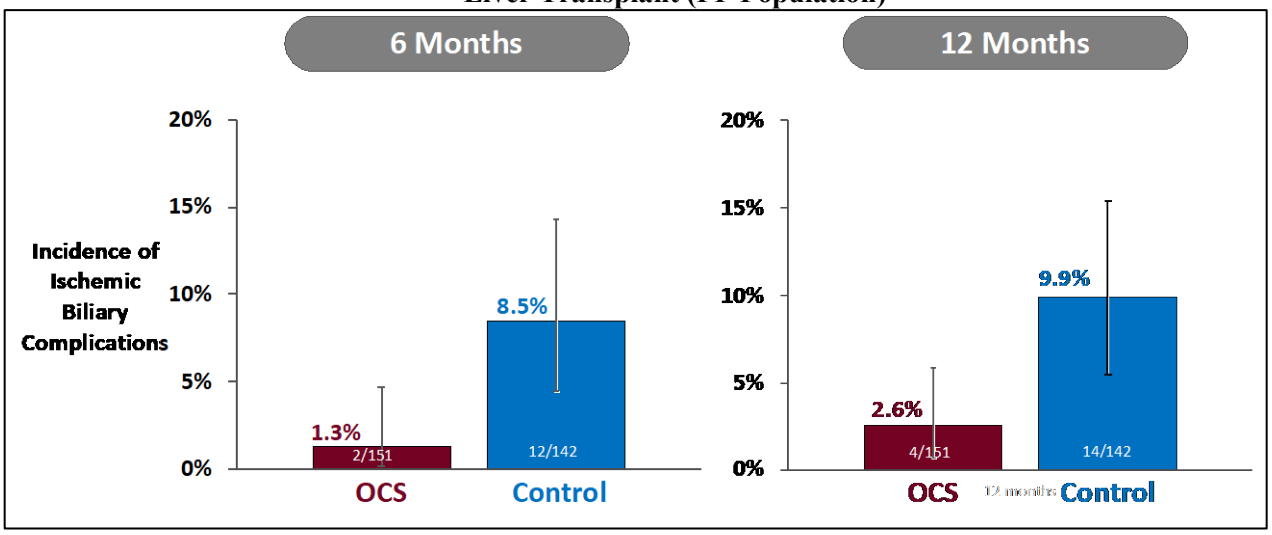
*Non-inferiority demonstrated with non-inferiority margin=7.5% and two-sided 90% CI

Other Clinical Endpoints

Incidence of Ischemic Biliary Complications at 6 and 12 Months

In the PROTECT trial, ischemic biliary complications were site reported based on clinical findings. A lower incidence of ischemic biliary complications was observed in the OCS arm compared to the Control arm at 6 and 12 months follow-up (Figure 13).

Figure 13: Incidence of Ischemic Biliary Complications Through 6 and 12 Months Post-Liver Transplant (PP Population)



At day 30 post-transplant, the rate of non-ischemic biliary complications was 8.5% for OCS compared to 4.1% for control, while the rate of post-transplant bile duct leak was 2.6% for OCS and 7.5% for control.

Assessment of Recipient Lactate Levels

Recipient mean lactate levels post-reperfusion were reduced in the OCS group compared to in the Control group based on an ad hoc analysis (Table 14).

Table 14: Recipients' Mean Lactate Levels Post- Transplant (PP Population)

Timepoint	OCS Recipient Arterial Lactate (mmol/L) Mean ± SD N=152	Control Recipient Arterial Lactate (mmol/L) Mean± 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

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 15). As seen in Figure 9, for most livers, the OCS Liver lactate trended down and then were stable during perfusion, indicating that the donor liver regained metabolic activity, although this did not result into a survival advantage for the OCS arm.

Table 15: 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
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

Ischemic Time

The use of the OCS Liver reduced the total cold ischemic time on the liver allografts by limiting the ischemic times to two time periods:

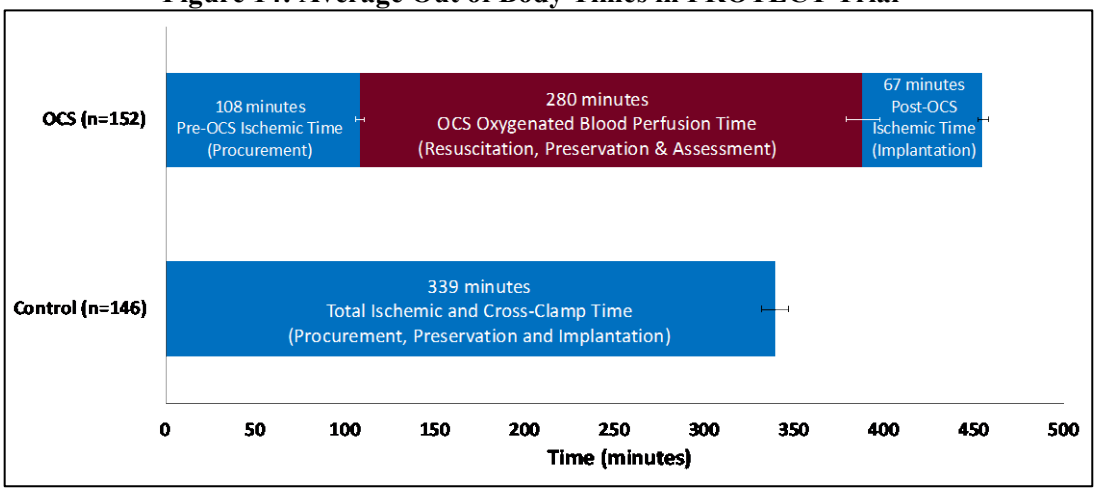
- Pre-OCS Ischemic Time: This is the time needed to surgically remove the donor liver from the body of the donor, perform the back table surgical preparation and instrument it on the OCS Liver. The OCS instrumentation takes ~10-15 minutes;
- Post-OCS Ischemic Time: this is the time needed to surgically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

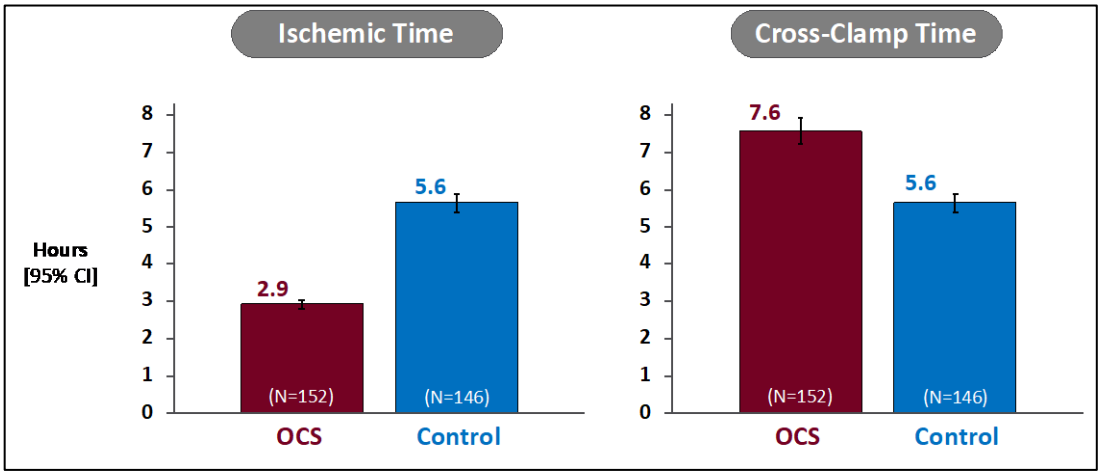
Figure 14 shows the average durations of these time windows in the PROTECT trial.

Figure 14: Average Out of Body Times in PROTECT Trial



The total ischemic time was reduced on the OCS Liver compared to Control, despite the OCS having longer total cross-clamp (out of body) time (Figure 15 below).

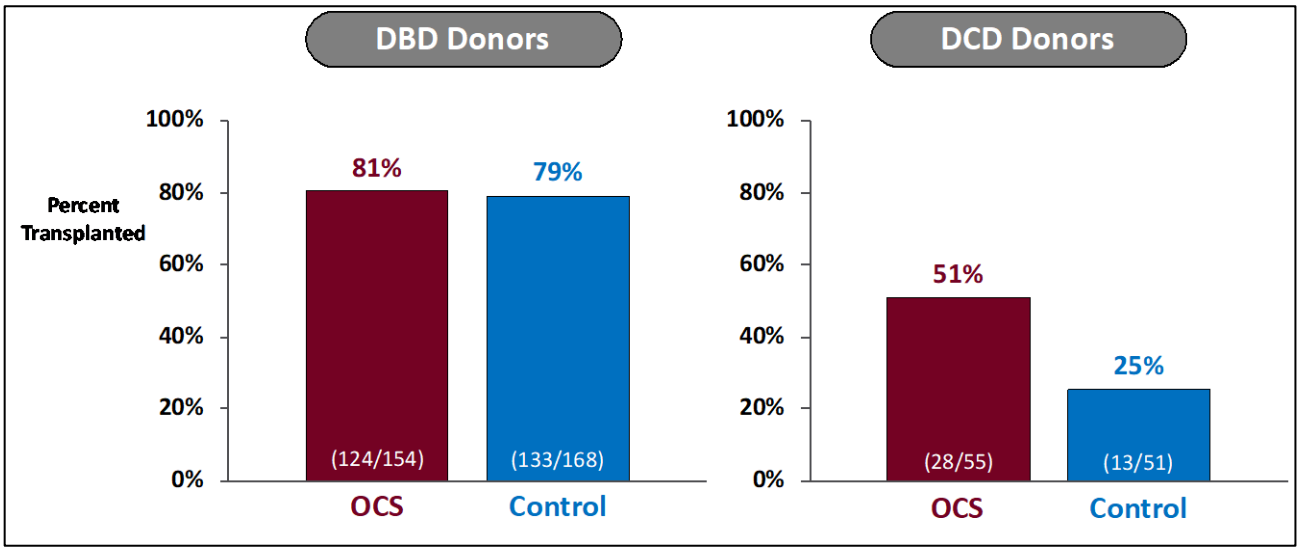
Figure 15: Total Ischemic and Cross-Clamp (Out of Body) Times in PROTECT Trial



Transplantation of DCD Donor Livers

Figure 16 shows that among 55 DCD livers matched to randomized OCS patients, 28 (51%) were transplanted while among 51 DCD livers matched to randomized control patients, 13 (25%) were transplanted. The proportion of DBD livers matched to randomized OCS patients that were transplanted was 81%, and the proportion transplanted in the Control arm was 79%.

Figure 16: Proportion of DBD and DCD Donor Livers Transplanted in PROTECT Trial



The OCS Liver provided additional opportunity for monitoring of hemodynamics and metabolic parameters of the DCD liver grafts, and a higher proportion of DCD livers transplanted was observed for OCS compared to the Control arm (51% versus 25%). The monitoring data provided by the OCS Liver during preservation allows the user to make an ex vivo assessment while the organ is being perfused.

Pathology Assessment

To assess the impact of ischemia and reperfusion (IR) injury associated with each preservation method, the PROTECT trial pre-specified that three donor liver tissue samples be examined blindly by an independent core pathology laboratory with extensive experience in liver transplant pathology. These three samples were:

- Sample 1: taken to assess the baseline condition of the donor liver prior to initiation of any preservation method.

- Sample 2: taken after preservation 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. This is the first time when IR injury is expected to manifest with OCS, because this is the first biopsy after organ reperfusion.

- Sample 3: taken after transplantation and reperfusion of the donor liver in the recipient, which makes it the most clinically relevant for IR injury. This is particularly true in the PROTECT trial because the preservation methods for OCS and Control differed substantially. This is the timepoint

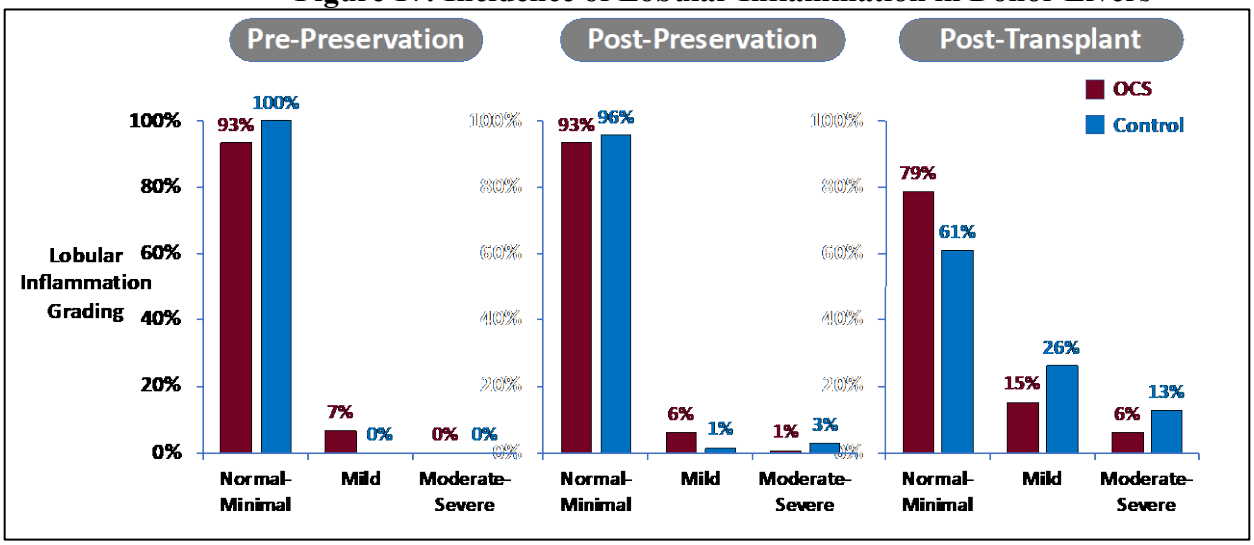
where IR injury would first manifest in donor livers on cold storage, because this is the first biopsy after organ reperfusion in the control group, while in OCS, donor livers had already been reperfused, oxygenated, and were metabolically active throughout preservation.

All samples were examined for lobular inflammation, which is a marker for IR injury and for lobular necrosis, which is a sign of irreversible damage of the liver tissue.

Lobular Inflammation

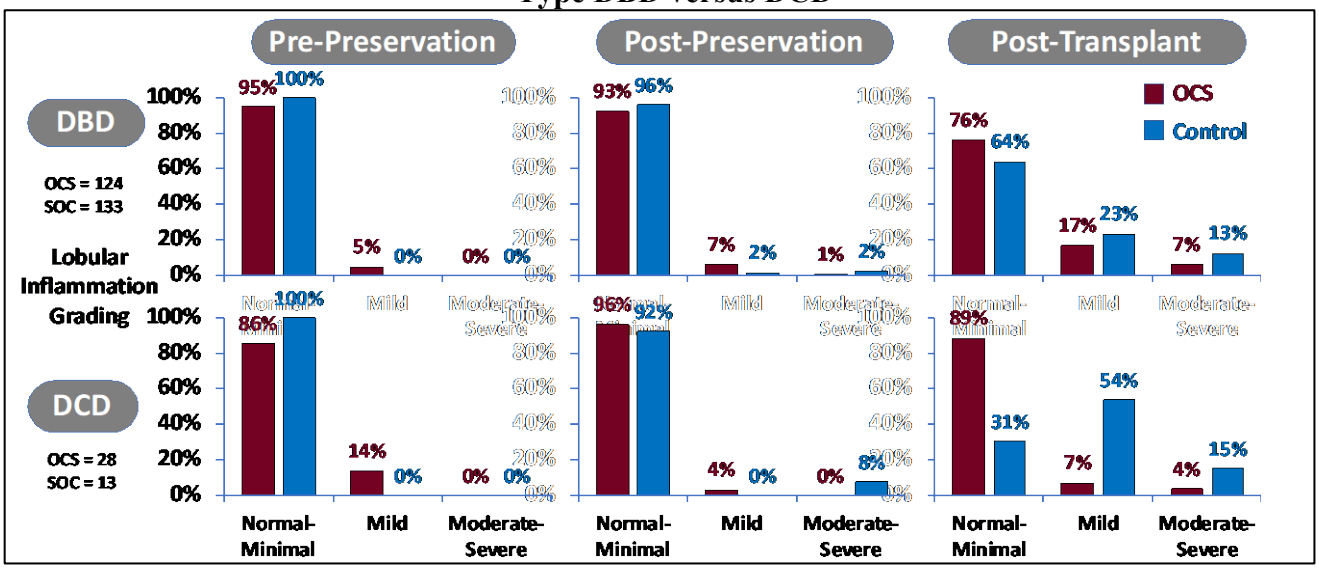
In this analysis, the pathological assessment demonstrated less lobular inflammation in post-transplant samples of the OCS preserved donor livers compared to Control arm (Figure 17).

Figure 17: Incidence of Lobular Inflammation in Donor Livers



The same finding of lower incidence of lobular inflammation was seen in both the DBD and DCD donor population post-transplant specimens in the PROTECT trial, see Figure 18 below.

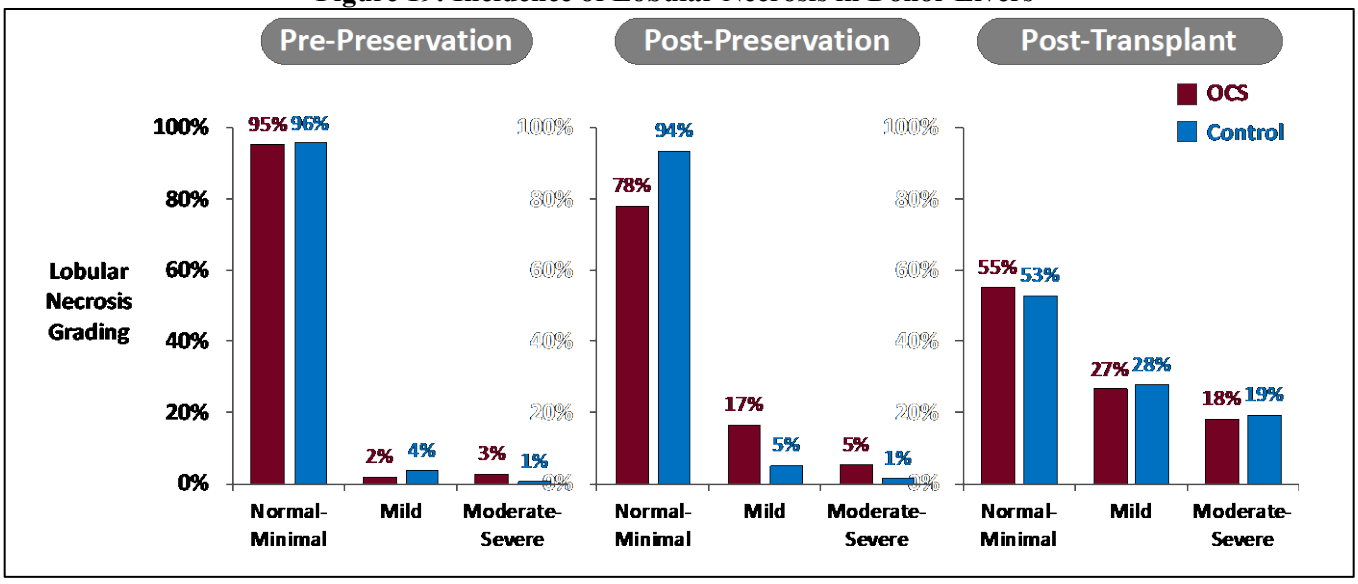
Figure 18: Incidence of Lobular Inflammation in Donor Livers Stratified by Donor Type DBD versus DCD



Lobular Necrosis

In this analysis the post-transplant pathological assessment demonstrated that lobular necrosis was equivalent between the two trial arms (Figure 19). Although, decreased lobular inflammation was noted in the OCS arm, no difference in necrosis was observed in the post-transplant samples.

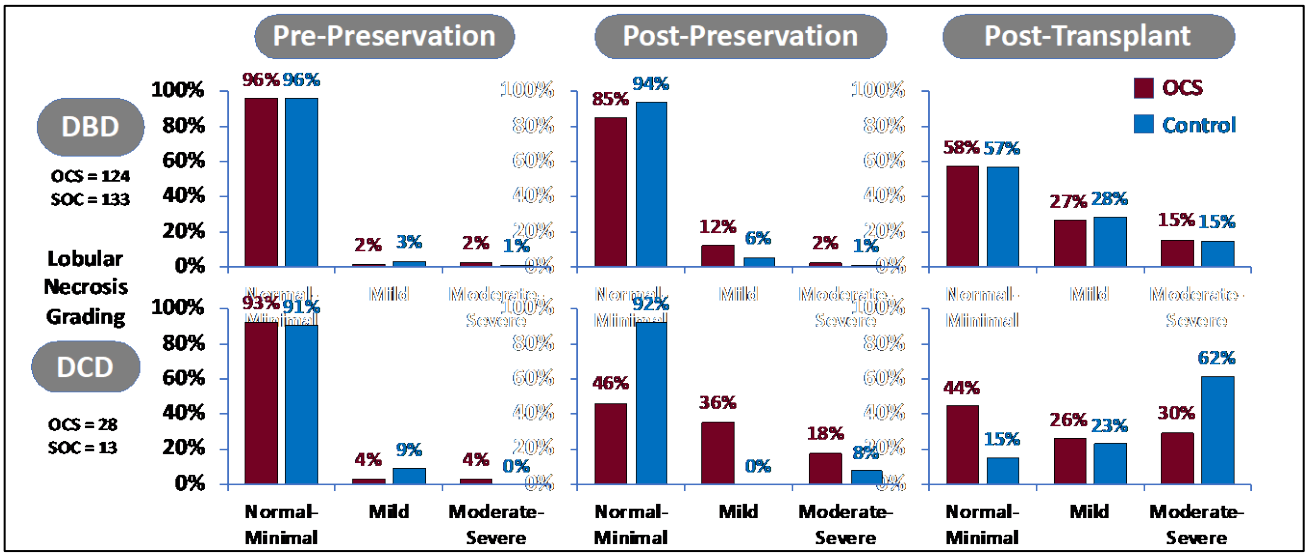
Figure 19: Incidence of Lobular Necrosis in Donor Livers



When the impact of donor type on this histological marker of irreversible liver damage was assessed, the DCD donor livers had a higher incidence of post-

transplant lobular necrosis as compared to DBD, and the OCS arm was associated with lower incidence of lobular necrosis in the DCD arm as compared to Control (Figure 20).

Figure 20: Incidence of Lobular Necrosis in Donor Livers Stratified by Donor Type DBD versus DCD



3. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 112 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY of SUPPLEMENTAL CLINICAL INFORMATION

OCS PROTECT Continued Access Protocol

The OCS Liver PROTECT Continued Access Protocol (CAP) was approved by FDA 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.

A total of 74 subjects have been enrolled in OCS Liver PROTECT CAP. As of the April 8, 2021, all 74 subjects have reached 30 days post-transplant, 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.

Donor Characteristics and Demographics

Donor demographics and characteristics are shown in Table 16 below. There have been no donor liver turndowns after OCS perfusion in the PROTECT CAP. The donor characteristics are similar to the OCS Liver PROTECT trial, except that PROTECT CAP has a higher percentage of DCD donors (23% in CAP) compared to PROTECT (18%).

Table 16: 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, n (%)	
• Anoxia	37/74 (50.00%)
• Cerebrovascular/Stroke	24/74 (32.43%)
• Head Trauma	12/74 (16.22%)
• CNS Tumor	0/74 (0.00%)
• Other [(1)]	1/74 (1.35%)
Donor Inclusion Criteria, [(2)] n (%)	
• Donor age ≥ 40 years old	50/74 (67.57%)
• Expected total cross clamp/cold ischemic time ≥ 6 hours	33/74 (44.59%)
• Donor after circulatory death (DCD) with age ≤ 55 years old	17/74 (22.97%)
• Steatotic liver greater than 0% macrosteatosis and less than or equal to 40% macrosteatosis at time of retrieval	37/74 (50.00%)
Multiple Donor Characteristics	43/74 (58.11%)
(1) Bacterial meningitis (2) Multiple donor characteristics (inclusion criteria) could be met.	

Recipient Demographic and Baseline Characteristics

Recipient demographic and baseline characteristics are shown in Table 17 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 17: 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, n (%)	
• History of diabetes	22/74 (29.73%)
• History of liver cancer	30/74 (40.54%)
Primary Diagnosis, n (%)	
• 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%)

Early Allograft Dysfunction (EAD)

EAD for all patients was adjudicated by the CEC and is shown in Table 18 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 18: EAD Results, OCS Liver PROTECT CAP

	OCS Subjects (N=74)
EAD, n (%)	19/74 (25.68%)
• AST level > 2000 IU/L within the first 7 postoperative days	15/74 (20.27%)

	OCS Subjects (N=74)
• 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%)

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 five deaths have occurred among the 74 patients. None of the deaths was related to the liver graft. Summary of the causes of deaths reported were as follows:

- Patient 1: 73 y.o. recipient with MELD score of 28, BMI of 40 and severely compromised cardiac function was transplanted with a DBD donor organ. Prior to liver implantation, experience cardiac arrest several times intra-operatively and experienced disseminated intravascular coagulation (DIC) and pulmonary embolism requiring tissue plasminogen activator (TPA) administration during the transplant procedure. Liver function was negatively impacted due to severe hemodynamic compromise and DIC due to cardiac arrest. Patient was re-transplanted on day 9. Patient expired on day 111 from generalized sepsis.
- Patient 2: 47 y.o. recipient with MELD score of 40 and diagnosis with alcoholic liver cirrhosis, was transplanted with a DBD donor organ. The patient expired on day 30 due to sepsis secondary to perforated duodenal ulcer.
- Patient 3: 73 y.o. recipient with MELD score of 28, was transplanted with a DBD donor organ. Patient expired on day 59 due to sepsis of respiratory origin.
- Patient 4: 57 y.o. recipient with MELD score of 15, transplanted with a DBD donor organ. Patient expired on day 75 due to respiratory failure secondary to pre-existing hepatopulmonary syndrome.
- Patient 5: 61 y.o. recipient with MELD score of 32, was transplanted with a DBD donor organ. Patient expired on day 108 from respiratory sepsis secondary to mycobacterium lung abscess.

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

Summary of PROTECT CAP Results

There has been 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.

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

A. Panel Meeting Recommendation

At an advisory meeting held on July 14, 2021, the Gastroenterology and Urology Device Panel Meeting TransMedics Organ Care System (OCS) Liver Panel voted 14/14 that there is reasonable assurance the device is safe, 14/14 that there is reasonable assurance that the device is effective, and 12/14 (1 No, 1 abstain) that the benefits of the device outweigh the risks in patients who meet the criteria specified in the proposed indication. https://www.fda.gov/advisory-committees/advisory-committee-calendar/july-14-2021-gastroenterology-and-urology-devices-panel-medical-devices-advisory-committee-meeting

B. FDA's Post-Panel Action

FDA worked interactively with the applicant to formulate the indications for use, labeling, and post approval study protocols to address recommendations by the Panel and the FDA.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The PROTECT trial demonstrated statistical superiority in reduction of EAD in the Per Protocol population compared to the Control arm. The OCS Liver PROTECT trial met the secondary effectiveness endpoint (OCS Donor Liver Assessment during Perfusion) and demonstrated that OCS Liver's capabilities for monitoring of lactate level, hepatic artery pressure, portal vein pressure and average bile production during preservation enabled monitoring of hemodynamics and metabolic function providing information that was used as part of surgeon decision-making to turn down livers for transplant. Despite the lower rate of EAD for the OCS arm compared to the Control arm, differences were not observed in clinically meaningful outcomes such as post-transplant ICU stay, initial hospital stay, and patient or graft survival.

B. Safety Conclusions

The OCS Liver PROTECT trial met its safety endpoint by demonstrating that the average number of LGRSAEs per patient in the OCS arm was statistically non-inferior to the Control arm. Lower ischemic biliary complications were observed compared to Control at 6 months post-transplant (1.3% for OCS vs 8.5% for control) and at 12-months post-transplant (2.6% for OCS vs 9.9% for control). While non-ischemic biliary complications, measured at 30 days, were higher in the OCS (8.5%) compared to the control (4.1%) while the rate of post-transplant bile duct leak was 2.6% for OCS and 7.5% for control. The risks of the device are based on data collected in a clinical study conducted to support PMA approval as described above.

The risks include device malfunction, although the rate reported in the PROTECT trial was low (3/155 1.9%) and no organs appeared injured or were deemed not transplantable due to any device malfunction. Three livers were also turned down in the OCS arm while no livers were turned down in the Control arm.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The primary effectiveness endpoint in the PROTECT trial was an assessment of EAD. The OCS treatment arm resulted in an absolute 14.5% difference in EAD (OCS 17.9%, Control 32.4%), which was found to be both non-inferior ($p<0.0001$) and superior ($p=0.0044$) according to the pre-specified analyses, compared to the Control. While this would appear to be a statistically and clinically significant benefit, there is uncertainty associated with this result. Although the primary endpoint of this study was the incidence of EAD, EAD is intended as a predictor of clinical outcomes[1], and it is less relevant as a proxy than the actual clinical outcomes of recipient and graft survival. In the study by Olthoff et al., EAD reliably predicted increased 6-month mortality and increased graft loss with an 8-10-fold difference between recipients with EAD versus the recipients without EAD. However, in the PROTECT Trial, despite a significant difference between the EAD rates at 7 days, no clinically or statistically significant differences between subsequent mortality or graft loss rates were observed. Given that host and graft survival are the most relevant measures of transplant success, the reduction in EAD in the OCS arm is of unclear significance. Despite the lower EAD rates in the OCS arm, there was not a correlation with other intermediate clinical outcomes (ICU stay, hospital stay) that might reflect a clinical benefit.

The assessment of EAD was based on, but was not exactly the same as, that described and validated by Olthoff et al.[1] A majority of recipients in the PROTECT trial (71.6%) were classified as having EAD by meeting the AST >2000 criterion (note that ALT levels were not included as part of the PROTECT trial primary endpoint's definition of EAD, but a subsequent post hoc analysis revealed no difference in EAD rate if ALT were considered), while a majority of recipients in the Olthoff study were deemed to have EAD based on the elevated bilirubin (Total Bilirubin ≥10 mg/dL on post-operative day (POD) 7) criterion. The relative contribution of each criterion to the severity of EAD events and their relatedness to outcomes such as survival are unknown. Hence, it is challenging to evaluate the severity of EAD. Therefore, it is unknown if the predominance of elevated AST, but not bilirubin or INR, as the criterion for EAD is the reason there is no observed concomitant survival benefit. It is also likely that the study was underpowered to assess differences in clinically relevant outcomes such as patient and graft survival with respect to EAD. It does not appear that EAD serves as a proxy for survival in the PROTECT trial, thereby minimizing the purported benefit of decreased EAD in the OCS arm of the trial.

The PROTECT trial met the secondary effectiveness endpoint (OCS Donor Liver Assessment during Perfusion) and demonstrated that OCS Liver's capabilities for

monitoring of lactate level, hepatic artery pressure, portal vein pressure and average bile production met the performance goal of 85% of donor livers preserved using OCS for the entire preservation period. Assessments were made for 144 out of 155 organs perfused on the OCS. However, there were no predefined transplantability criteria, and none of these parameters, including change in perfusion fluid lactate, liver enzymes, and bile output and concentration have been validated or shown to correlate with clinically relevant outcomes such as graft or recipient survival.

In the PROTECT trial, the sponsor reports an increase in the number of DCD donor livers transplanted in the OCS arm compared to the Control arm (OCS 50.9% (28/55), Control 25.5% (13/51)). However, there is uncertainty associated with this purported benefit due to limited data (only 41 out of 298 livers, 13.8% mITT population) and an imbalance between treatment arms, because more DCD organs were included in the OCS arm. The study design did not include stratification to ensure that an equal number of DCD organs were included in each arm. Furthermore, the PROTECT trial was open-label and the investigators had knowledge of the treatment assignment. Given the uncertainties in this limited subgroup analysis, no claims in increased DCD donor organ utilization can be made.

In the PROTECT trial, the sponsor also claims that the device resulted in a reduction of ischemic biliary complications, reperfusion syndrome, and lobular inflammation. However, even though these analyses were pre-specified as "Other Endpoints" in the Statistical Analysis Plan, they were not included in the multiplicity adjustment procedure and therefore, no statistical inference can be drawn for these "Other Endpoints."

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. Use of the OCS device adds a risk of organ turndown when compared to the standard of care. In the PROTECT trial, the sponsor asserted that assessment of the organ while on the device resulted in clinical benefits such as identifying lower quality DCD livers that were unacceptable for transplant due to rising lactate and bridging fibrosis. However, it is unclear if these organs were damaged prior to being placed on the OCS-Liver, or if the damaged was caused after being placed on the OCS-Liver. Furthermore, criteria for suitability for transplant based on these parameters monitored by the OCS device are not established. The risk of donor organ turndown impacted one recipient in the PROTECT trial who underwent unnecessary anesthesia prior to the donor organ turndown. No potential recipients underwent unnecessary incision.

Use of the OCS device also adds a risk of device malfunction when compared to the standard of care. However, in the PROTECT trial, the rate of device malfunctions was low (3/155, 1.9%) and this risk is mitigated thought the conversion of the donor organ from the OCS Liver to cold storage.

Additional factors to be considered in determining probable risks and benefits for the Organ Care System (OCS™) Liver device included: donor organ and recipient

disposition and trial design issues. Of the 476 donor livers uniquely matched to randomized recipients, 176 (37%) were considered as screening failures by the sponsor and were excluded from the PROTECT trial. Similarly, of the 429 consented (428 randomized) subjects, 129 (30%) were excluded from the PROTECT trial and did not have any primary and secondary endpoint data collected. Of those excluded subjects, 49 (11% of total) were transplanted outside of the trial and not followed, 43 were transplanted outside the trial with survival data. Due to the high proportion of post-randomization exclusion, these recipient and donor liver disposition issues increased the uncertainty associated with the trial results described above.

In conclusion, the device preserves donor DBD and DCD livers ≤55 years old and with ≤30 mins of warm ischemic time, macrosteatosis ≤15%, comparably to the cold, static, storage standard of care with similar graft and patient survival, with the additional probable benefit of decreased ischemic biliary complications and, importantly, the ability to monitor the organ during preservation which provides the transplant surgeon with additional information whereby to assess the organ prior to transplantation. The benefit of decreased EAD is unclear given the lack of correlation with patient or graft survival, but the PROTECT trial may have been underpowered to detect such differences. The additional risks of device malfunctions with their implications to the recipient in terms of donor organ transplantability and unnecessary procedures are considerable but no such outcomes were evidenced in the PROTECT trial. Serious consequences of device malfunction are mitigated by the opportunity to convert to cold storage which is explained in the device labeling. Further information will be gathered in the post-approval study. In addition, an increased rate of non-ischemic biliary complications was noted for the OCS arm. The mechanism is unclear but might be due to increased instrumentation required to place the donor organ on the OCS Liver device. Again, further information will be gathered in the post-approval study. Additional uncertainty was introduced by the randomization scheme, which may be necessitated by the complex nature of transplant clinical trials. While this could introduce bias, and while it may even exist in the conduct of this trial, there is no direct evidence of bias was introduced into the trial because of this issue. The lack of transplantability criteria allows for the subjective use of the available monitoring data by the transplant surgeon and raises questions about the consistency of future turndown decisions. However, a greater number of DCD livers ≤55 years old, with ≤30 mins of warm ischemic time, and macrosteatosis ≤15% were implanted, potentially due to the availability of this additional information to the transplant surgeon. There is enough uncertainty around the association between the use of the OCS Liver and DCD utilization that there should be no claim around increased DCD utilization rates due to the device.

The benefits, as described above, outweigh the risks for the indications for use while acknowledging the uncertainty associated with both benefit and risk in the available data, considering additional mitigations including labeling directives and, importantly, additional data generated by the post-approval study.

1. Patient Perspective
   This submission either did not include specific information on patient

perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for the indication, *The TransMedics® Organ Care System (OCS™) Liver is a portable extracorporeal liver perfusion and monitoring system indicated for preservation and monitoring of hemodynamics and metabolic function which allows for ex vivo assessment of liver allografts from donors after brain death (DBD) or liver allografts from donors after circulatory death (DCD) ≤55 years old and with ≤30 mins of warm ischemic time, macrosteatosis ≤15%, in a near-physiologic, normothermic and functioning state intended for a potential transplant recipient,* the probable benefits outweigh the probable risks.

D. 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, which limit the use of the device to specific DCD donor organs that were enrolled in the PROTECT trial (e.g., DCD livers ≤55 years old and with ≤30 mins of warm ischemic time, macrosteatosis ≤15%).

XIV. CDRH DECISION

CDRH issued an approval order on September 28, 2021. The final clinical conditions of approval cited in the approval order are described below.

1. OCS Liver PROTECT Continuation PAS (Protocol Number OCS-LVR-01-PAS, Rev. 1.0, dated September 14, 2021):

The OCS Liver PROTECT Continuation PAS is an observational study designed to evaluate long-term outcomes in the PROTECT trial cohort. The 300 patients who were randomized to the OCS and Control (cold storage) arms in the PROTECT trial will be followed up to 2 years post-transplant. The primary effectiveness endpoint is liver graft survival at 24 months post-transplant. The other study endpoint is patient survival at 24 months post-transplant.

The timelines for the PROTECT Continuation PAS are as follows:

- Complete 2-year follow-up on all PAS participants by November 30, 2021
- Submit a Final Report by February 28, 2022

2. OCS Liver PROTECT CAP Continuation PAS (Protocol Number OCS-LVR-02-PAS, Rev. 1.0, dated September 14, 2021):

The OCS Liver PROTECT CAP Continuation PAS is an observational study designed to evaluate long-term outcomes in the PROTECT CAP cohort. Seventy-four subjects who were transplanted with OCS-preserved livers in the CAP study will be followed through

2 years post-transplant. The primary effectiveness endpoint is liver graft survival at 24 months post-transplant. The other study endpoint is patient survival at 24 months post-transplant.

The timelines for the PROTECT CAP Continuation PAS are as follows:

- Complete 2-year follow-up on all PAS participants by March 31, 2023
- Submit a Final Report by June 30, 2023

3. OCS Liver Perfusion (OLP) New Enrollment PAS (Protocol Number OCSLIVER-01-PAS, Rev. 1.0, dated September 16, 2021):

The OLP registry is a multi-center, single-arm, observational study designed to evaluate the short- and long-term safety and effectiveness of the OCS Liver for DBD and DCD donor livers preserved on OCS according to the approved indication. To evaluate real-world use of the device, the OLP registry will include all liver transplant centers in the U.S. that will commercially use the OCS Liver, with a minimum of 15 sites enrolled.

The PAS will enroll the initial 160 sequential adult primary liver transplant recipients who are transplanted with an OCS-perfused DBD or DCD donor liver according to the approved indication. If the initial 160 recipients do not include at least 60 DCD donor liver transplants, the OLP registry will continue to enroll only DCD donor liver recipients until 60 DCD recipients have been enrolled. This is to ensure adequate assessment of device performance in DCD donor livers. PAS participants will be followed for 2 years post-transplantation and all analyses will be stratified by DBD and DCD donor populations.

The primary endpoint is patient and graft survival at 1 year. The safety endpoint is liver graft survival at 6 months. Additional clinical endpoints include: incidence of ischemic, non-anastomotic biliary complications through 1-year; incidence of non-ischemic, anastomotic biliary complications through 6 months; Kaplan-Meier estimates for patient survival at 1- and 2-years; and Kaplan-Meier estimates for graft survival at 6 months, 1- and 2-years.

In addition to the patient outcomes listed above, the following data will be collected: OCS Liver perfusion parameters (hepatic artery flow and pressure, portal vein flow and pressure, perfusate temperature, perfusate hematocrit, and perfusate venous saturation); lactate levels; pH value at beginning and end of OCS perfusion; total bile volume at end of OCS perfusion; incidence of and clinical reasons for donor liver turndown following OCS perfusion; incidence of and reasons for conversion to cold storage after initiation of OCS perfusion; device malfunctions that are routinely obtained from customer complaints and MDRs; and the donor liver utilization rate.

The primary analysis population will be comprised of the first 160 sequential patients who meet the approved indication for use according to adjudication by the Clinical Events Committee (CEC). For the primary endpoint, this study will test the hypothesis

that 1-year patient and graft survival in the PAS is greater than a performance goal of 83.5%. This study will also test the hypothesis that 6-month graft survival is greater than a performance goal of 85.5%. The full PAS cohort will continue to be followed for 2 years, for evaluation of all study endpoints using descriptive analyses.

From the time of study protocol approval, the timelines for the OLP New Enrollment PAS are as follows:

- First patient enrolled within 6 months
- 20% of patients enrolled within 15 months
- 50% of patients enrolled within 21 months
- 100% of patients enrolled within 33 months
- Submission of Final Report 3 months after study completion (i.e., last enrolled patient completes 2-year follow-up)

In addition, separate periodic reports on the progress of the OLP New Enrollment PAS will be submitted as follows:

- PAS Progress Reports every 6 months until subject enrollment has been completed, and annually thereafter.

If any enrollment milestones are not met, the applicant must begin submitting quarterly enrollment status reports (i.e., every 3 months), in addition to periodic (6-months) PAS Progress Reports, until FDA notifies the applicant.

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

[1] Olthoff KM, Kulik L, Samstein B, Kaminski M, Abecassis M, Emond J, Shaked A, Christie JD.Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. Liver Transpl. 2010 Aug;16(8):943-9. doi: 10.1002/lt.22091.