FDA Executive Summary

Prepared for the **July 14, 2021**
Meeting of the
Gastroenterology and Urology
Device Panel

(b)(4)

TransMedics® Organ Care System™ (OCS) Liver System

Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

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1. Synopsis/Introduction

This document provides a summary of the clinical and nonclinical data submitted by TransMedics, Inc., in support of the Premarket Approval (PMA) (b)(4) for the TransMedics® Organ Care System™ Liver System™ (OCS-Liver) manufactured by TransMedics, Inc. The OCS- Liver is a portable system for near-normothermic continuous perfusion of donor livers with the perfusate being prepared by the hospital's pharmacy, and addition of ABO compatible packed red blood cells (pRBCs). The sponsor proposes that the OCS-Liver device can preserve donor after brain death (DBD) or donor after circulatory death (DCD) liver allografts in a temperature controlled (34°C), near-physiologic and functioning state from the time of organ retrieval until transplantation into a recipient.

Cold flush and cold static storage is the standard of care for preservation of donor livers. The preservation time period usually does not exceed 10-12 hours. Currently there are no FDA-approved devices for use in normothermic machine liver perfusion. There are several FDA-cleared solutions (Belzer UW®, Custodial® HTK, Celsior®, Bel-Gen, SPS-1®, Viaspan, and Servator H SALF) indicated for cold flush and cold static storage of livers. The TransMedics® Organ Care System™ Lung System™ was approved for use in standard lungs in 2017 and extended criteria lungs in 2019.The TransMedics® Organ Care System™ Heart System™ went to panel on April 6, 2021 and is currently under review. The current device intended for livers, differs in several technological characteristics as well as the organ intended for preservation.

The Advisory Panel will be asked to discuss a benefit/risk evaluation of the clinical data submitted in this PMA to demonstrate reasonable assurance of safety and effectiveness of the OCS-Liver when compared to the existing standard of care for liver preservation during transplantation, cold flush and cold static storage. There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence[2], that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.[3] There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.[4]

A pivotal trial, the PROTECT trial, was conducted with the OCS Liver System under investigational device exemption (IDE) number (b)(4) . The PROTECT trial was a prospective, multi-center, randomized trial of 300 recipients from 20 US transplant sites randomized 1:1 to the OCS-Liver or standard of care (Control), cold, static storage. The trial began January 24, 2016 and was closed to recipient enrollment on October 15, 2019. Thirty-day follow-up was completed on November 19, 2019 and the last 6-month follow-up was on March 28, 2020. Updated data including 12-month follow-up was provided with a cut-off date of October 15, 2020.

A single arm PROTECT Continued Access Protocol (EXPAND CAP) was approved on 11/14/2019 under (b)(4) *to permit continued use of and adjunctive data collection to support the OCS Liver System while the PMA* (b)(4) *was under review. TransMedics submitted preliminary endpoint results to FDA based upon the 74 transplanted EXPAND CAP recipients; only limited datasets and no supporting source documentation for these CAP recipients were available for FDA review. These data*

should also not be pooled because the CAP trial had no control. Therefore, FDA only presents a short summary of the data on the CAP trial in Section 8.0 of this executive summary.

The Executive Summary for this Advisory Committee Meeting of the Gastroenterology and Urology Device Panel on the OCS Liver System includes the non-clinical and clinical data that has been provided by the sponsor in the PMA (b)(4) application. In particular, the clinical sections:

- Summarize the PROTECT trial design, results, and conclusions derived from the use of the OCS Liver System for livers;
- Provide a summary of FDA's evaluation of the device's safety and effectiveness data; and
- Discuss the Agency's concerns regarding this PMA application and the PROTECT trial data, including:
    - Limitations of the clinical study, including screen failures and "dry runs"
    - Clinical considerations of the primary effectiveness endpoint early allograft dysfunction (EAD), the dominance of transaminase (AST) as a driver of EAD, and the recipient and graft survival results
    - Implications of device use in terms of pathology, device malfunctions, and organ turndowns
    - Adequacy of clinical data to support use of this device for donor after circulatory death livers (DCD).

2. Proposed Indications for Use

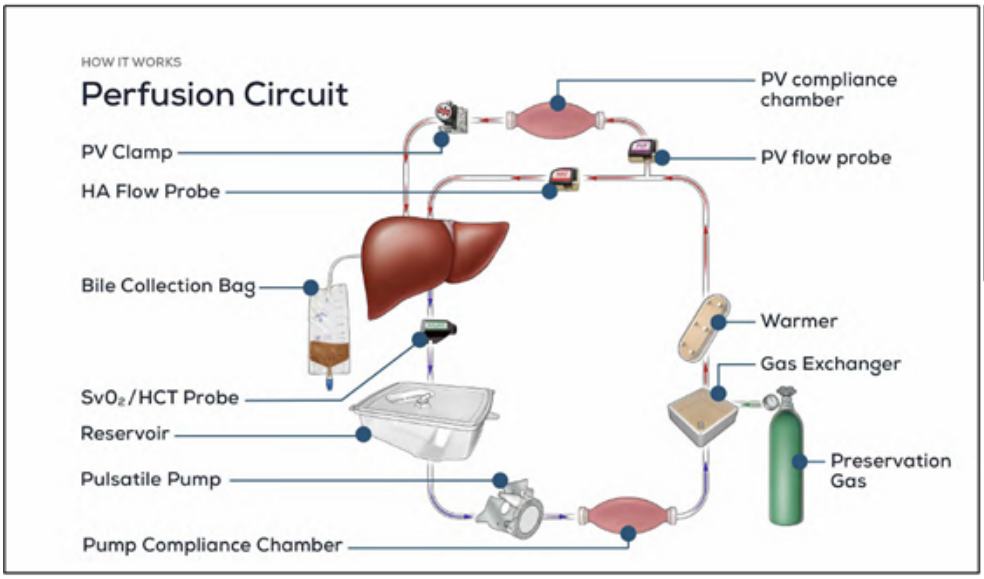
TransMedics proposes the following indications for use statement for the OCS Liver System:

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

3. Device Description

The Organ Care System Liver is a device designed to transport donor livers from the donor site to the transplant recipient site by using extracorporeal circulation to maintain liver viability via continuous organ perfusion with temperature controlled, oxygenated blood and perfusate. The current standard-of-care (SOC) preservation method involves flushing the liver with a cold organ preservation solution, packing the liver in a sterile and hypothermic container, and transporting the liver to the recipient's transplant center. OCS preservation aims to minimize the cold-ischemic time (CIT), which can be up to 12 hours for healthy livers. A schematic of the OCS Liver System perfusion fluid flow path is shown in Figure 1 below.

Figure 1. Schematic of OCS Liver System Fluid Flow



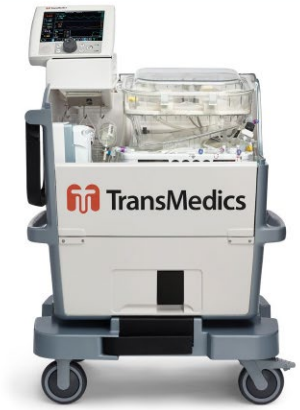
PV – Portal Vein
HA- Hepatic Artery
$Sv0_2$/HCT – Mixed venous hemoglobin saturation
HCT - Hematocrit

The TransMedics® OCS Liver System is composed of three major components:

- OCS Liver Console: the portable enclosure that houses the non-sterile, reusable components (e.g., electronics) of the OCS Liver System.
- Liver Perfusion Set (LvPS), which consists of two subparts:
    - Liver Perfusion Module (LvPM): the sterile disposable circuit, which perfuses, maintains physiologic environment, and optimizes and monitors the perfusion parameters and bile production.
    - LvPS Accessories: the sterile disposables for instrumenting and managing the perfusate.
- OCS Liver Bile Salts Set: Composed of sodium taurocholate, which is infused into the circulating perfusate to replenish the bile salt levels during perfusion.

Photographs of the three main components of the OCS Liver System are shown in Figure 2 below.

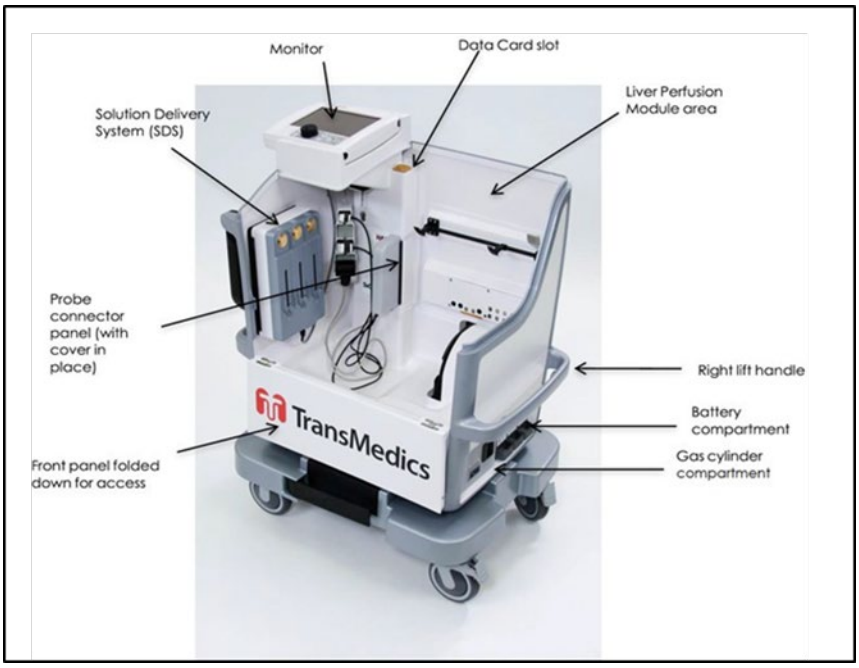
Figure 2. OCS Liver System Components

OCS Liver Console	OCS Liver Perfusion Set	OCS Liver Bile Salts
		

3.1 Liver Console

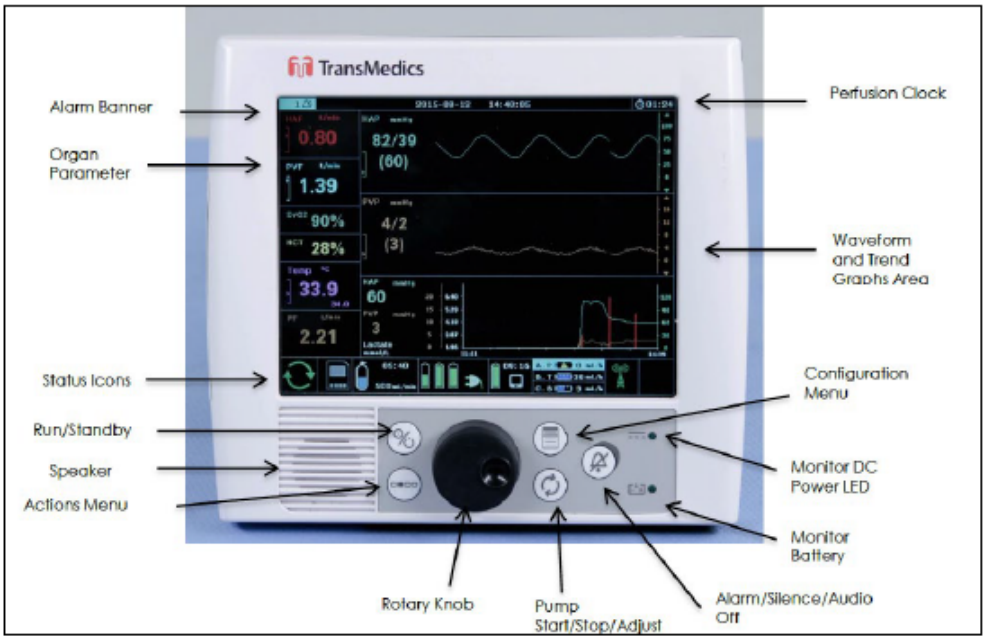
The OCS Liver Console is a non-sterile, reusable portable enclosure that houses the infusion and circulatory pump, the batteries, electronics, gas delivery components, blood warmer, pressure, flow and saturation meters, and wireless monitor. The wireless monitor allows the clinical operator to control and display critical perfusion parameters of the preserved donor Livers. The OCS connects to its mobile base for transport, which is shown in Figure 3 below:

Figure 3. OCS Liver Console with Cover Removed



The wireless monitor that communicates with the liver console to track the vital functions of the organ being perfused is shown in Figure 4 below. It can be physically connected to the console or removed and used via a commercially available Bluetooth connection.

Figure 4. Wireless Monitor



The OCS Liver System circulates temperature-controlled (34°C) pRBCs/perfusate through an oxygenator, to provide oxygen and nutrients to the donor liver during transportation of the donor organ to the recipient site. Throughout OCS support, the user can adjust blood flow rate, solution delivery flow rate, gas flow rate, and blood temperature to optimize the perfusion environment for the donor organ, through direct measurements of hepatic artery pressure (HAP), portal vein pressure (PVP), hepatic artery flow (HAF), portal vein flow (PVF) and pump flow (PF), which is a combination of HAF and PVF. Mixed venous hemoglobin saturation percentage (SvO_2), hematocrit percentage (HCT) and perfusate temperature (TEMP) are also reported on the wireless monitor. The performance specifications for these parameters are shown in Table 1 below. An off-the-shelf portable blood gas analyzer is utilized to check blood chemistry and lactate. Lactate levels are measured and are used as an indicator of adequate perfusion of the donor organ throughout preservation. The perfusion parameters are monitored and adjusted as needed throughout the duration of support on the OCS Liver, with adjustments based on lactate level and trend.

Table 1. Select Performance Specifications for the OCS Liver System

	Specifications
Heating Capabilities	
Temperature Settings	34.0 – 37.0 ºC
Temperature Maintenance	Maintain temperature 34°C ± 2°C at an ambient temperature of 25°C ± 0.5°C
Temperature Rise Time	(b)(4)
Gas Delivery	
Flow Rate	(b)(4)
Accuracy	(b)(4)
Liver Gas	(b)(4)
Solution Delivery	
Flow rate	1 – 99 mL/min
Flow type	Positive displacement
Solution Delivery Modes	Manual and Off

The wireless monitor includes several alarms as described in the Tables 2 and 3 below.

Table 2. Alarms for the OCS Liver System

Indicator	Meaning
Low Gas Remaining	Less than 60 Minutes of Liver Gas Remaining at the configured flow rate
Low OCS Battery	Less than 30 Minutes battery power remaining
Low Wireless Monitor Battery	Less than 30 Minutes battery power remaining
System Fault Alarm (e.g., Wireless Monitor Communication Link Failure)	Immediately

Table 3. Alarm Limit Ranges and Defaults

Function*	Units	Alarm Limit Range	Default Lower Limit	Default Upper Limit
HAF	L/min	0.20-1.05 L/min	0.30 L/min	0.60 L/min
PVF	L/min	0.45-2.05 L/min	0.50 L/min	1.50 L/min

SvO_2	%	55-95%	70%	n/a
HCT	%	16-30%	20%	n/a
Blood Temperature	ºC	33-38°C	33.5°C	34.5°C
PVP	mmHg	0-15 mmHg	4 mmHg	10 mmHg
HAP	mmHg	40-150 mmHg	65 mmHg	100 mmHg
*Note: There are no alarms for PF, as it is combination of HAF and PVF.				

The Liver Console contains a circulatory pump or pulsatile pump to circulate the perfusate. The user controls the perfusate rate through the wireless monitor and the cycle rate of the pump and displacement of the pump head determine the perfusate flow. The pump is shown in Figure 5 and pump specifications are shown in Table 4.

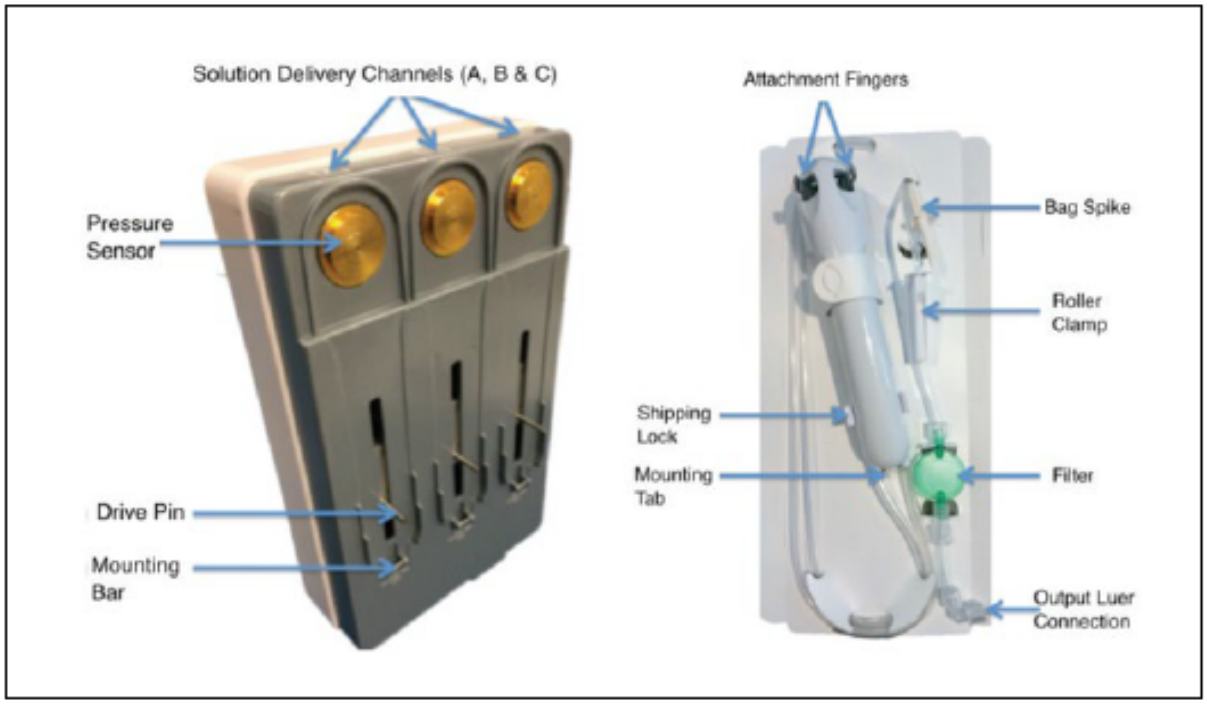
Figure 5. OCS Liver System Circulatory Pump

Table 4. Select Specifications for the Pumping Systems

Pump Type	Specifications
Circulatory Pump	
Flow Rate Type	Pulsatile
Pump Cycle	Systolic phase and diastolic phase with a nominal rate of 60 beats per minute
Pump Mode	Asynchronous
Range of flow rates	250 to 3,500 mL/min

The Liver System includes a Solution Delivery System (SDS) that is used to administer solution to the LvPM during organ preservation. The system includes the SDS console and SDS line sets. The SDS is a 3-channel component that operates similar to a refillable syringe pump. The pump provides a means of adding solutions to the system at user-configurable rates. The SDS line set is sterilized and single-use. The SDS console and line set is shown in Figure 6 below.

Figure 6. Solution Delivery System onsole and line set.

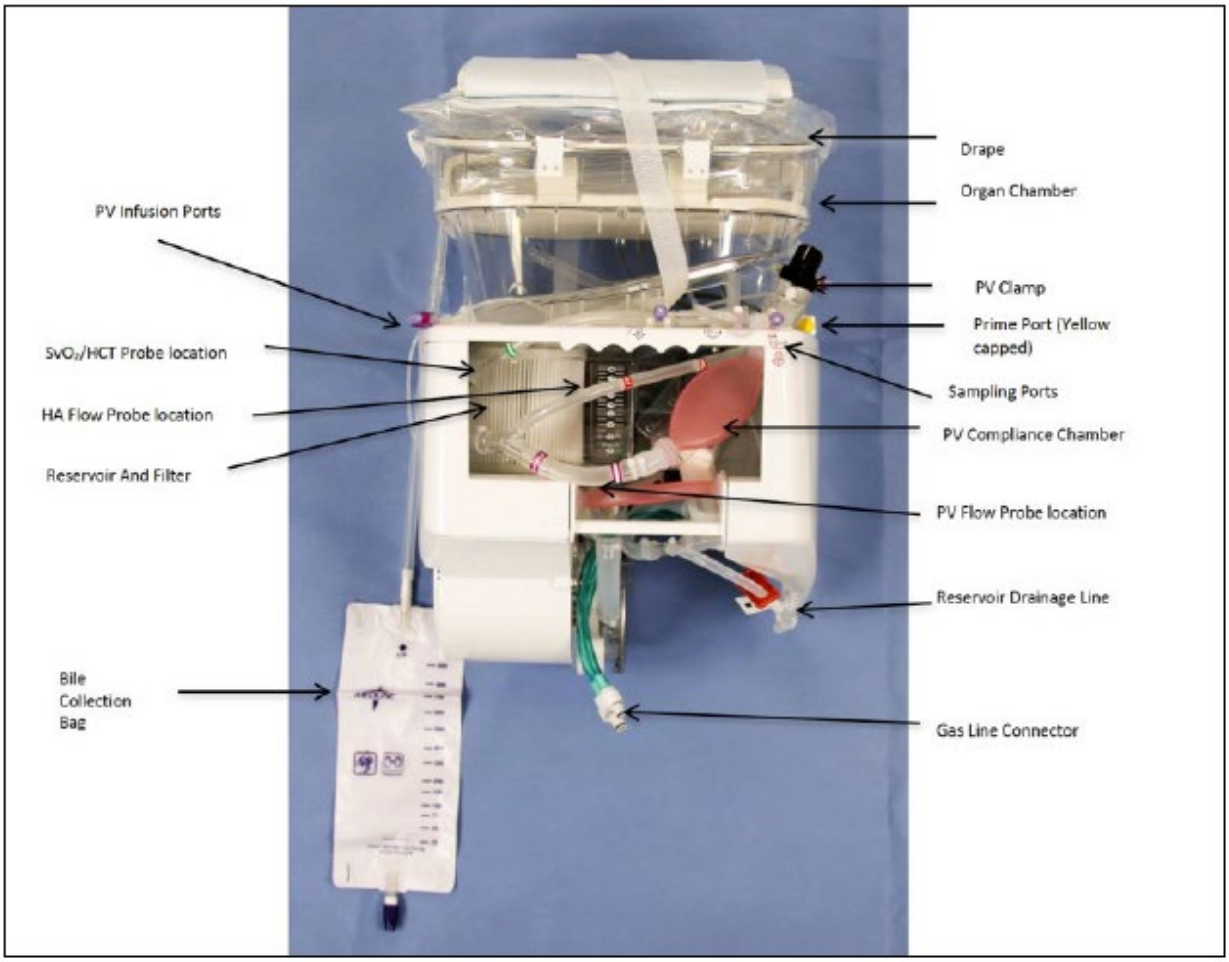


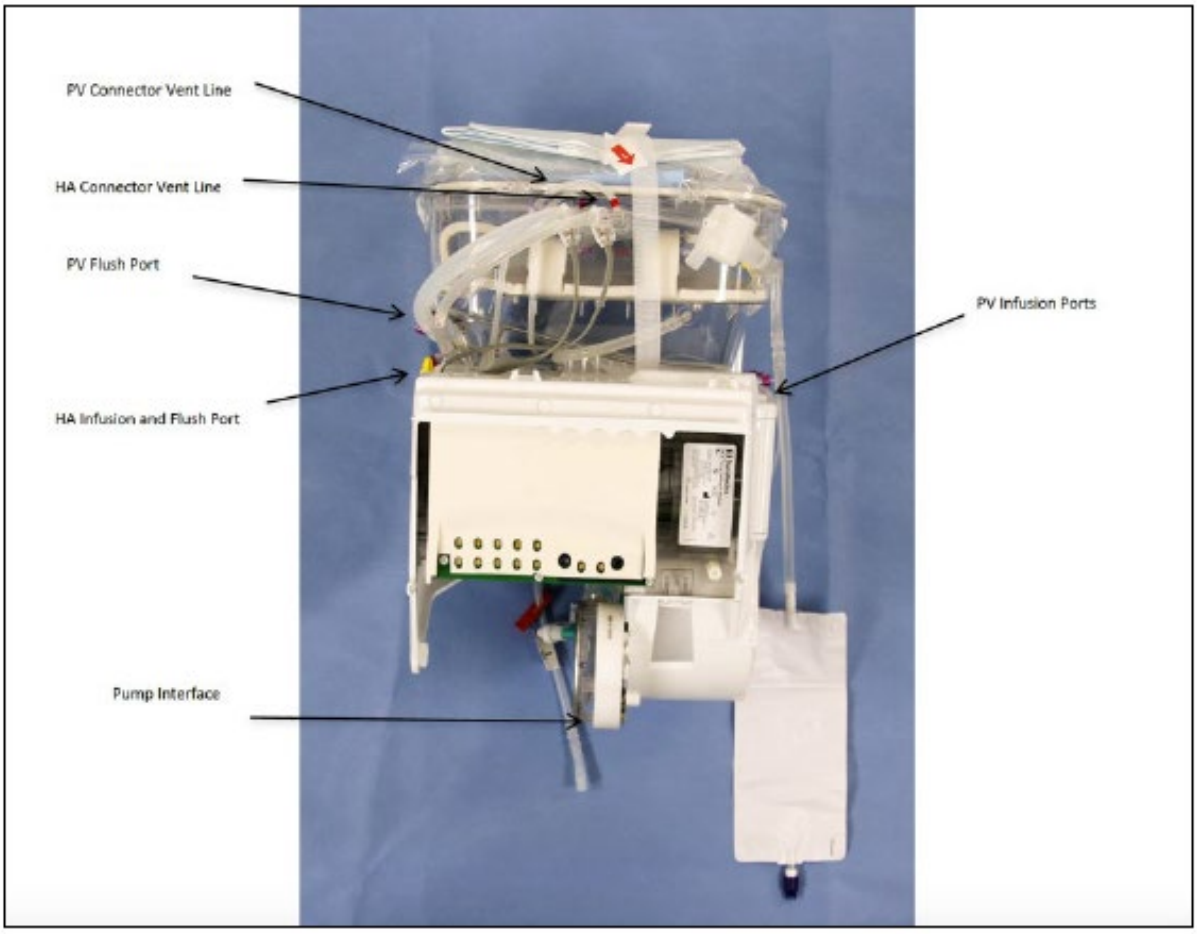
3.2 Liver Perfusion Set consists of Liver Perfusion Module (LvPM) and Liver Perfusion Accessories (LvPS)

The Liver Perfusion Set consists of the Liver Perfusion Module (LvPM) and LvPS accessories. The LvPM, shown in Figures 7 and 8 below, is a sterile, single-use device that holds and maintains the liver during preservation and transport. This module contains all the perfusate and organ-contacting components and interfaces with the console.

Figure 7. The Liver Perfusion Module inside the Liver Console

Figure 8. LvPM components Front View (top) Back View (Bottom)

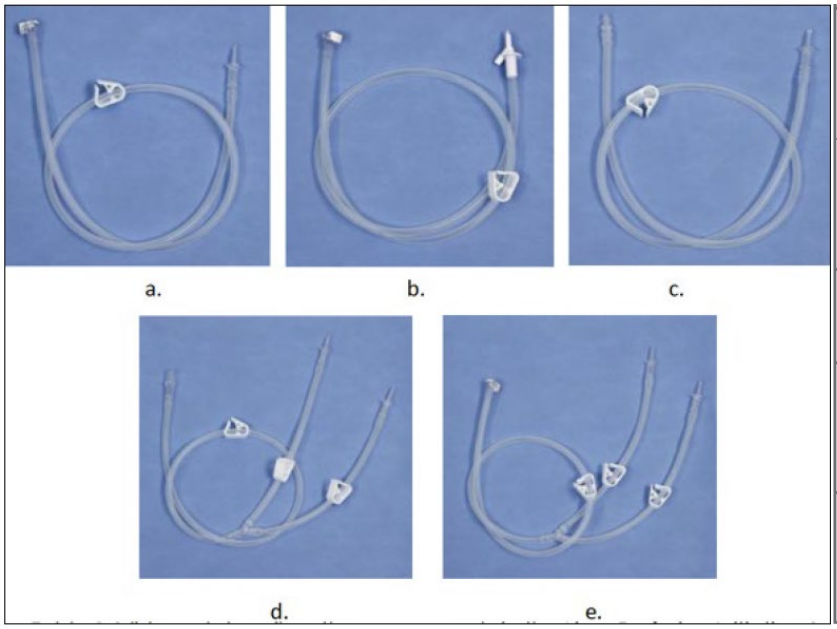




The Liver Perfusion Accessories (LvPS) include many components used for perfusion initiation, cannulation, infusion, and perfusion termination. These accessories are shown in Figures 9-12 below. The LvPS also includes the bile salts that are supplied to the user by TransMedics. The OCS Liver Bile Salts Set is comprised of two vials of gamma sterilized bile salts (Sodium Taurocholate) with 1 g per vial. The bile salts are reconstituted before use with sterile water for injection. Then the solution is infused into the LvPM circuit through the Liver Solution Infusion Set and controlled by the SDS. The perfusate containing the bile salts is flushed from the system and donor liver prior to transplantation. A photograph of the bile salts is shown in Figure 11 below.

- Liver Perfusion Initiation Set is used at the beginning of the perfusion procedure to introduce the perfusate (b)(4) to the reservoir and to flush the liver prior to preservation.

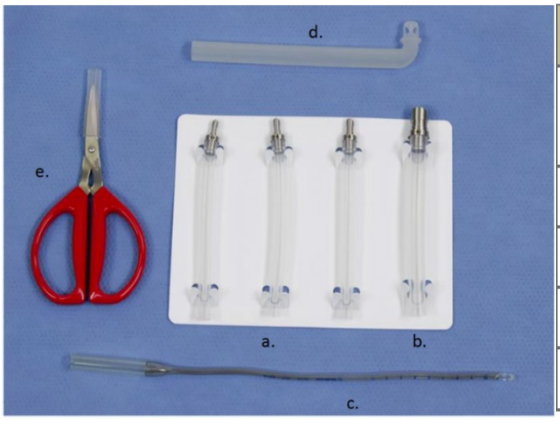
Figure 9. Liver Perfusion Initiation Set



a.	Quick Prime Line
b.	Albumin Prime line
c.	HA Initial Flush Line
d.	PV Initial Flush Line
e.	Dual Blood Prime Line (2)

- Liver Instrumentation Tool Set – includes sterilized accessories for instrumenting the liver to the system.

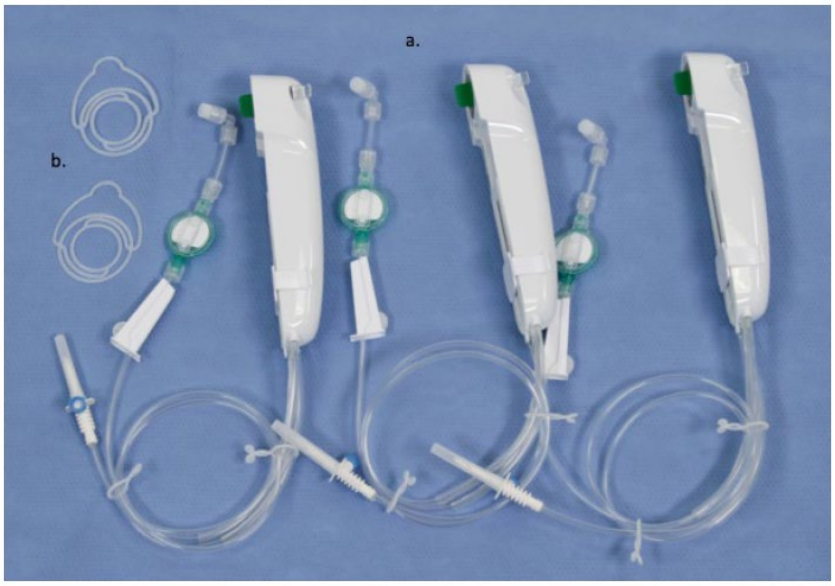
Figure 10. Liver Instrumentation Tool Set Components



#	Item
a.	HA Cannula
b.	PV Cannula
c.	Bile Cannula
d.	IVC Cannula
e.	Tube Cutter

- Liver Solution Infusion Set – includes three sterilized SDS Line Sets and bottle holders.

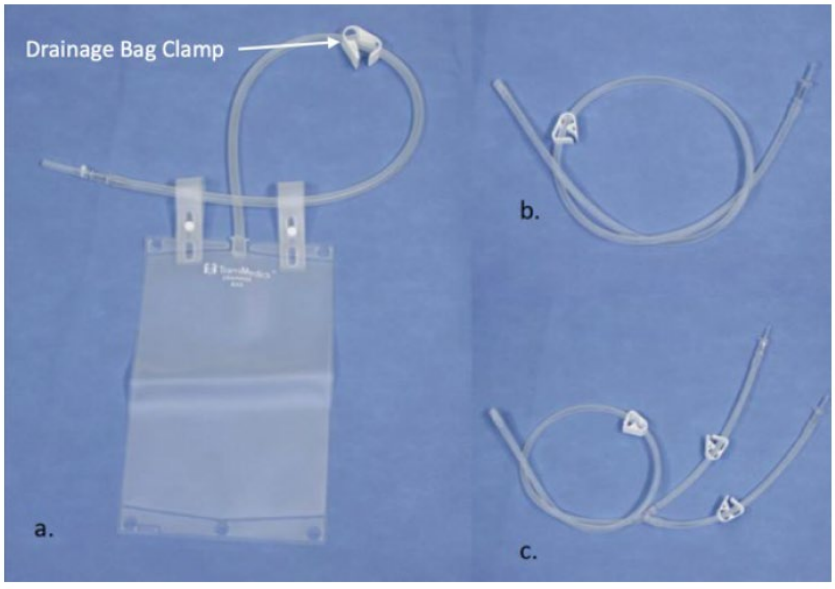
Figure 11. Liver Infusion Set Components



a.	SDS Line Sets (labeled as Liver Solution Delivery Cassette) (3)
b.	Bottle Holders (2)

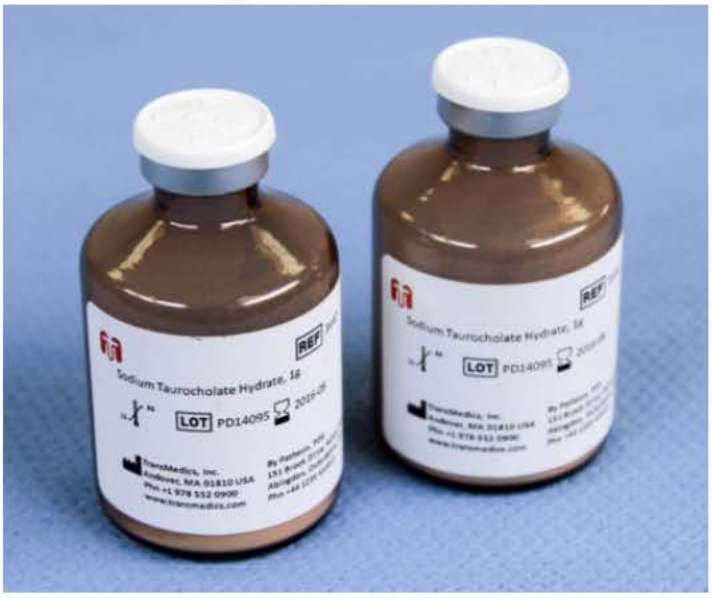
- Liver Perfusion Termination Set – includes the final flush lines for the HA and PV and a drainage bag for removing the solution from the Liver Console. This set is used at the end of the perfusion procedure.

Figure 12. Liver Perfusion Termination Set



a.	Liver Drainage Bag
b.	HA Final Flush Line
c.	PV Final Flush Line

Figure 13. Bile Salts Set



3.3 OCS Liver Solution and Additives

The perfusion solution, additives and infusions are provided by the user. Table 5 further explains the solutions, additives, and infusions used during liver transplantation in the PROTECT trial.

Table 5. Solution Additives and Perfusate Infusions Supplied by User

	Purpose
Priming Solution/Perfusate Components	
(b)(4)	
Perfusate Additives	
(b)(4)	
Infusions to Perfusate (added through SDS infusion*)	

(b)(4)

*Note that reconstituted OCS Liver Bile Salts are also administered to the organ through the SDS; however, TransMedics provides the OCS Liver Bile Salts.

3.4 Principles of Operation

Instrumentation of Donor Liver

If the donor liver is deemed acceptable using the inclusion criteria described in Section 6 of this document, the liver is initially flushed in the donor body using cold Belzer UW® solution or Custodial® HTK preservation solutions. An organ to be transplanted to the recipient randomized to the OCS arm will then be flushed on the back table using (b)(4)

The OCS liver is assembled for use by connecting the LvPM to the console and is primed with perfusate provided in Table 5. The pump circulates the perfusate through the circuit to prime and de-air the LvPM, as well as activate gas flow and blood warming. After priming, the liver is instrumented on the OCS and the hepatic artery (HA), portal vein (PV), inferior vena cava (IVC) and common bile duct are cannulated to the corresponding ports inside the organ chamber. The perfusion clock is started, and the pump flow (b)(4)

The recommended ranges provided in (b)(4) are shown in Table 6 below. Note the red values indicate the values that were used in the PROTECT trial. The sponsor states that these changes reflect knowledge gained during the trial and that investigators found that "broader ranges were needed to reflect the diversity in liver vascular tone that can be observed based on donor factors, such as age, DCD status, etc."

Table 6. Preservation Ranges

Parameter	Range
Hepatic Artery Pressure (HAP):	(b)(4)
Hepatic Artery Flow (HAF):	
Portal Vein Pressure (PVP):	
Portal Vein Flow (PVF):	
Perfusate Temperature (Temp):	34°C

Oxygen Gas Flow:	(b)(4)
Circulating Arterial Lactate Trend:	stable or trending down over time
Bile Salt Infusion	(b)(4)

*Red values indicate ranges used in PROTECT pivotal trial (b)(4)

An arterial blood sample is measured within the first 30 minutes to measure lactate levels, arterial blood gas (ABG), and pH. The user is instructed to check the bile duct for bile production. If the liver is producing bile and everything is going according to procedure the organ is wrapped and secured for transport.

Maintenance of Donor Liver

The OCS Liver is intended to perfuse and maintain donor livers during transportation to the recipient site. If the HAP target is achieved with stable lactate, then a vasodilator infusion will be maintained at the lowest flow rate to maintain HAP. Once HAP is maintained, the liver is ready for transport. During transport and preservation, the instructions state the liver should be maintained according to the parameters shown in Table 6.

ABG, lactate, and liver enzymes are then collected from the arterial port of the OCS perfusion circuit. During the PROTECT trial, ABG and lactate samples were collected approximately every hour until the lactate was trending down and then collected every two hours or after any active HAF or HAP adjustments. Liver enzymes (Aspartate Transaminase (AST), Alanine Aminotransferase (ALT), gamma-glutamyl transferase (GGT) and lactate dehydrogenase (LDH) were collected in addition to ABG and lactate immediately before cooling the organ prior to reimplantation.

Arresting the Donor Liver and Removal from the OCS Liver System

In accordance with the clinical trial protocol, the donor liver is assessed at the recipient site. After the final arterial blood sample is retrieved, the user will check the stability of the organ perfusion parameters, specifically looking at stable or trending down lactate levels and bile production rate. Prior to removing the liver from the OCS, (b)(4)

The OCS organ chamber is then opened, and the liver is disconnected from the OCS. After removal, the surgeon prepares that donor liver for transplantation in accordance with standard surgical procedures. The OCS Liver System then undergoes a shutdown procedure. The LvPM is disposed of and the console is prepared for storage.

4. Regulatory History

Prior to submitting the current PMA for the OCS Liver (b)(4) TransMedics submitted several other related applications to FDA, including investigational device exemptions (IDEs), and a pre-submission (Q-SUB). Table 7 shows the applications submitted to FDA that are directly related to the OCS Liver System. The (b)(4) (DCD Liver trial) is actively enrolling patients but results from this trial are not included in this PMA application.

The initial IDE for this first-in-human Liver near-normothermic machine perfusion device was approved as a staged trial design after the sponsor provided animal safety data. A *staged approval*[1] provides an opportunity to continue collecting safety data in parallel as enrollment is initiated. Enrollment in the first phase of the trial began on January 24, 2016. The first 20 recipient safety data submission was provided to the FDA in October 2016, and FDA granted expansion of the pivotal trial to

> The panel will be asked whether the OCS Liver System adequately assesses donor livers to make decisions regarding subsequent transplantation of the donor livers.

25 U.S. institutions and 300 U.S. recipients on November 16, 2016.

Table 7. FDA Submissions Related to the OCS Liver System

FDA Application	Application Content	Overview
(b)(4)	OCS Liver PROTECT trial	FDA approved the trial on 7/9/15 for 20 U.S. recipients at 20 sites (Part A). FDA approved an expansion to 40 U.S. recipients on 9/16/16 under (b)(4). FDA approved an expansion to 300 U.S. recipients at 25 U.S. sites on 11/16/16 under (b)(4) (PART B). The OCS Liver PROTECT trial is a randomized, controlled pivotal trial, comparing donor livers preserved by standard of care (on ice) with donor livers preserved on the OCS Liver System.
(b)(4)	OCS Liver PROTECT Continued Access Protocol (CAP)	FDA approved the CAP for 74 U.S. recipients at 21 U.S. sites on 11/14/19 under (b)(4) Trial enrollment has been initiated. - The purpose of this trial is to allow continued access to the OCS Liver System during PMA development and review.
(b)(4)	OCS Liver DCD trial	FDA approved the trial for 130 U.S. recipients at 20 U.S. sites on 11/26/19. The objective of this trial is to evaluate the safety and effectiveness of the OCS Liver System to preserve, optimize the condition, and assess livers from DCD donors that currently are seldom used for liver transplants due to limitations of cold static storage with extended warm ischemic time and older donors.
(b)(4)	OCS Liver DCD trial	Q-Sub for OCS Liver System that included a Breakthrough Device Request. Breakthrough Device status granted by FDA for the Liver DCD indication on 12/6/19.

4.1 PROTECT Trial Milestones and Device/Protocol Changes

Several minor changes were made to the device during the PROTECT trial and were approved in supplements to (b)(4); these changes are considered minor and are not expected to result in clinical outcome differences.

Several changes to the clinical protocol, shown in Table 8, were also made during the PROTECT trial including changes made to address some of FDA's trial design considerations communicated to the sponsor in the (b)(4) staged-approval letter. However, several outstanding trial design

considerations remained outstanding at the end of trial enrollment.

Table 8. Number of Recipients Enrolled under TransMedics' Protocols

Protocol Version	Application/Supplement	Date Received	Recipients Enrolled
Version 1.0	(b)(4)	September 30, 2014	N/A, protocol not released to site
Version 1.1	(b)(4)	January 12, 2015	N/A, protocol not released to site
Version 1.2	(b)(4)	June 18, 2015	0, protocol released to site, but no recipients transplanted
Version 1.3	(b)(4)	December 15, 2015	11
Version 1.4	(b)(4)	May 20, 2016	289

4.2 PROTECT Trial Study Design Considerations (SDC)

In 2012, Congress revised Section 520(g) of the Food Drug and Cosmetic Act such that,

> "*FDA will not disapprove an IDE because the investigational plan for a pivotal trial may not support approval or clearance of a marketing application. However, if FDA believes modifications to the trial are needed to achieve this objective, FDA will convey such considerations to the sponsor to provide greater clarity and predictability. In addition, FDA will convey to the sponsor considerations that FDA believes will be important for future submissions related to the proposed investigation.*"[1]

Approval of an IDE is largely based on safety of the trial recipients. Typically, concerns about clinical trial design that do not affect safety of recipients in the trial are communicated to the sponsor of an IDE as "Study Design Considerations (SDC)" and "Future Concerns (FC),"[1] usually as an enclosure to the IDE letter. While FDA recommends that the study design considerations are addressed in a timely manner (to provide a dataset that can support a marketing application), the IDE sponsor is not required to respond to the study design considerations, and the sponsor can complete their trial without addressing the study design considerations.

FDA provided many outstanding SDCs and FCs and the sponsor addressed several of them during the early stages of the trial. Several PROTECT trial annual reports indicated numerous screening failures in the OCS arm. The early imbalances in screening failures raised concerns about trial integrity. Many of these failures were due to the presence of accessory vessels in donor Livers randomized to the OCS arm of the trial. The sponsor explained that a contributing factor to this imbalance is a lack of attention by the investigators to the presence of accessory vessels in the control arm. The sponsor retrospectively reviewed the operative reports of the control arm recipients to determine which control arm livers contained accessory vessels. The sponsor further defined reported screened and randomized patients that were not transplanted and returned to the waitlist for re-randomization as dry runs and these recipients were no longer designated as screening failures. These early issues in screening failure imbalances are discussed in more detail in Appendix 1.

There are several SDCs that were outlined in letters to the sponsor, which were not entirely resolved

during the PROTECT trial. These issues are also discussed elsewhere in this Executive Summary. FDA's recommendations included the following:

- To eliminate "early randomization" and randomize recipients after procurement of donor livers, and assessment for trial eligibility. Randomization to trial arm took place at the time of matching an available donor liver to a Waitlist (WL) consented recipient. The agency considered this "early randomization" to be prone to selection bias, because organ retrieval and final evaluation had not happened at this point, and the Principle Investigator was aware of the preservation method assignment (knowing the preservation method could potentially influence organ evaluation/rejection). This concern is magnified when the organ is transplanted outside of the trial and there is no further information on the outcomes of these livers excluded fromthe PROTECT trial but subsequently transplanted using cold, static storage.

- To include recipient and graft survival at 1-year post-transplantation as secondary effectiveness endpoints.

- To clearly designate screening failures (screening failures were mostly due to the presence of accessory vessels) and to provide follow-up outcomes and maintain, and report detailed narratives of all screening failures, including the disposition of the intended recipient and indexed organ. The sponsor collected some information on trial screening failures but as discussed further below, information was not available for all recipients transplanted off trial.

- To include all biliary complications as Serious Adverse Events (SAEs) used to assess the safety endpoint and not just ischemic biliary complications. The PMA submission includes an exploratory analysis of all biliary complications reported as SAE's in the trial.

- To include appropriate secondary endpoints that evaluate the correlation between the OCS device's measured and displayed parameters and any clinical outcomes to support the sponsor's proposed indication for use of "assessment" of the livers while on the OCS-Liver device.

- To reach agreement on pre-specified multiple testing procedure for superiority and non-inferiority of primary and secondary endpoints for type I error control, in support of labeling claims regarding secondary endpoints.

- To look for consistency among primary outcomes using the reported analysis populations (PP, mITT, and ITT) when testing non-inferiority and superiority of OCS vs. Control. An intent-to-treat population (ITT) consists of all recipients who have signed informed consent, been enrolled in the trial, randomized, and the assigned liver preservation method has been initiated; mITT includes all randomized and transplanted recipients.

FDA Comment: The Agency recommended trial randomization begin after the surgeon evaluated the recipient and the donor liver at retrieval and accepted the donor and liver recipient for transplantation without knowing the preservation method assignment. The basis for this recommendation was to avoid the potential for selection bias and dry runs by returning the potential recipient back to the WL for re-randomization. For further details on this topic please refer to Appendix 1.

5. Non-Clinical Testing

5.1 *In Vitro*/Bench Testing

Applicable *in vitro* testing has been performed, and results were acceptable. Testing included electrical safety testing, electromagnetic compatibility, battery testing, sterility, packaging, packaging integrity testing, shelf life testing, biocompatibility, software, cybersecurity, system operational testing, individual component testing, mechanical design verification, shock, vibration and altitude testing on the OCS Liver System, the OCS Liver Console, and the Liver Perfusion Set (LvPM plus LvPS Accessories). Major changes made during the trial were evaluated by risk analyses, and relevant testing was performed.

5.2 *Ex Vivo* Animal Studies

In (b)(4) , TransMedics provided FDA with data on a novel device design validation trial evaluating two *ex vivo* porcine livers preserved on the OCS Liver System for 12 hours, including transport in a vehicle for a minimum of 30 minutes. A near-final version of the device was used. HAP, HAF, PVP and PVF were maintained within device operating specifications. Liver function tests (aspartate aminotransferase, alanine aminotransferase), bile production, pH, lactate, and perfusate cultures were monitored. The perfused organs were not transplanted, and histologic evaluation of the livers was not conducted. There was no standard of care control arm in this study. Perfusion parameters were reportedly maintained within those specified for clinical use and all organ assessments improved or remained stable during preservation. This novel PMA study was intended only to validate device design changes.

The sponsor previously submitted four additional porcine *ex vivo* liver studies using an earlier version of the OCS Liver System, to support initiation of clinical trials (b)(4) . Phase 1 and Phase 2 animal studies provided proof-of-concept data with n=33 porcine *ex vivo* livers preserved for 8-12 hours followed by either no reperfusion (n=28) or four hours of reperfusion (n=5). Liver function tests were conducted, and lactate and bile production were monitored. Histologic evaluations were conducted but the lack of a pathology report and inadequate image quality limited FDA's ability to independently verify the results. No control arm was included in these studies. Outcomes of this testing supported liver function tests were acceptably maintained on the device for up to 12 hours and were leveraged to validate device design.

Prior to initiation of the PROTECT trial, Phase 2 animal testing was expanded to evaluate n=6 test and

n=6 control *ex vivo* porcine livers for 8 hours preservation followed by 4 hours simulated reperfusion.

The panel will be asked whether the OCS Liver System adequately assesses donor livers to make decisions regarding subsequent transplantation of the donor livers.

Control livers were maintained as per standard of care static cold storage (Control). Organ perfusion parameters were maintained within system specifications. Liver biomarker and histologic assessments supported the OCS liver System results in equivalent or better liver function as compared to the control arm. Bile production for the control arm was less than the OCS Liver System arm in the Phase 2 expanded trial, which included only limited liver function tests and only four hours simulated transplant time.

Phase 3 animal testing was conducted using n=3 *ex vivo* porcine livers each in the test and control arms. Test livers were preserved for 12 hours, followed by 24 hours simulated transplant/reperfusion. Organ perfusion parameters were maintained within system specifications. Liver biomarker and histologic assessments generally supported equivalent or better liver function for the OCS Liver System as compared to the control arm. Notably, bile production for the control and OCS Liver System arms was equivalent in the Phase 3 trial. The Phase 3 trial was primarily leveraged to initiate the PROTECT trial.

Animal studies were non-GLP and were conducted without a quality assurance unit. The sponsor noted the impracticality of performing animal testing at an outside facility given the complex nature of the OCS Liver System and the need for specialized personnel with expertise in trial procedures as justification for animal studies not being in compliance with GLP recommendations.

The sponsor states that the OCS Liver System enables the *ex vivo* assessment of organ viability via liver function tests, lactate levels, and bile production, as validated and supported by pre-clinical testing and the clinical results of the OCS Liver PROTECT trial. FDA notes that these preservation assessments, including change in perfusate lactate, liver enzymes, and bile production, have not been validated or shown to correlate with clinically relevant outcomes such as graft or recipient survival. Additionally, as none of the *ex vivo* livers in the animal trials were transplanted, it is challenging to leverage the data from these trials to validate that organ assessments during preservation on the OCS Liver System are predictive of clinical organ viability or translate to improvements in transplant success rates.

6. Clinical Studies

6.1 Clinical Background

Liver transplantation is universally accepted as the only curative treatment option for end-stage liver disease. The current recipient and graft survival rate for a primary liver transplant at 12 months post transplant are 91.8 and 89.6% respectively.[2] However, the availability of donor liver allografts has not kept pace with the demand. According to the 2019 Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) report, there were 12,767 new waiting list registrations and 8,896 transplants performed.

MELD score

The Model for End-Stage Liver Disease (MELD) score is calculated using clinical labs (serum creatinine, ((SCr), Bilirubin, and INR) and ranks potential liver recipients, according to their severity of liver disease and mortality risk on the OPTN liver waiting list. As shown in Table 9, the MELD score can accurately predict 3-month mortality among recipients with chronic liver disease on the liver waiting list and can be applied for allocation of donor livers.[3]

Table 9 MELD Score and Mortality

Wiesner et. al., N= 3437. OPTN WL data.		
MELD Score	3-month mortality in WL	Mortality in WL plus too sick for transplant
<9 (3.6%)	1.9 %	2.9%
10-19 (52.3%)	6 %	7.7%
20-29 (32%)	19.6 %	23.5%
30-39 (8.5%)	52.6 %	60.2%
>40 (3.5%)	71.3 %	79.3%

Transplant-related survival benefit is defined as the life expectancy with transplantation minus the life expectancy without transplantation. As shown in Merion et. al., the effect of transplantation on survival benefit varied across the range of MELD scores with significant transplant survival benefit observed at MELD scores 18 and higher, and the magnitude of transplant benefit increased with increasing MELD score.[4]

Graft and recipient survival have improved despite including donors with older age, higher MELD scores, and higher prevalence of obesity and diabetes.

Recipients aged 50-64 years make up over half (53.8%) of adults on the waitlist (WL) while older recipients (aged ≥65 years) represent 20.8% of adults on the WL in 2019. Most WL recipients have an initial MELD score <15 (47.1%), or 15-24 (36.3%), higher MELD scores are less frequent.

Despite the high demand for donor livers, not all consented deceased donor livers are utilized; SRTR/OPTN data shows that the overall discard rate of livers retrieved for transplantation is around 10%. The most common reason for discarding consented livers is biopsy findings (43.5%). Of these biopsy findings, moderate fatty change (defined as 30 to 60 percent fat content) was associated with the development of early allograft dysfunction.[5] Prolonged warm ischemia (6.6%), poor organ function during donor evaluation (5.7%), and prolonged cold ischemia (1.6%) are less frequent causes for discarding a consented liver. Other risk factors for EAD and causes for discarding consented donor liver are older age, donor hypernatremia, hemodynamic instability refractory to dopamine, and cold ischemic time (CIT) > 18 hrs.

The SRTR/OPTN 2011 registry shows one-year recipient and graft survival rates for liver transplantation approaching 90% and 85%, respectively and a half-life of 12.6 years for deceased donor liver transplantation. More recently, SRTR/OPTN 2019 graft survival only shows minimal improvement.

The lack of suitable livers results in a 13-month median wait-time to liver transplant despite the MELD score policy, as described below in Table 10. Using current static cold storage techniques, the graft failure rate during the first 6 weeks after transplantation is 5.53% for DBD donors, and 6.99% for DCD donors. To face the scarcity challenge, the use of ′extended criteria′ (also called 'marginal' or 'high risk') donor livers has been adopted by permitting liver donors with identified risk factors for poorer outcome.[6]

Endpoints in Liver Preservation:

FDA expects the endpoints in liver preservation studies to measure the effect of the new preservation method on ischemia reperfusion injury, EAD, graft loss, and other claimed benefits. EAD after liver transplantation is considered an early outcome measure[7] that has been shown to correlate with intermediate and long-term outcomes. EAD has been reported in the range of 2% to 36% depending on the EAD definition and population characteristics.[8,9] These data refer to static cold storage using several preservation solutions and a mix of standard and extended criteria donors. See table 9 below.

Olthoff KM, et.al.[10] validated the current criteria defining EAD in liver transplant recipients as AST or ALT >2000 IU/L within first-week post-liver transplant (LT), total bilirubin ≥10 mg/dL, and/or international normalized ratio (INR) ≥1.6 on post-operative day seven. The Olthoff trial found an overall incidence of EAD of 23.2%. Most grafts (including standard and extended criteria) met the definition with increased bilirubin at day 7 followed by high levels of aminotransferases. Of recipients meeting the EAD definition, 18.8% died within 6 months, as opposed to 1.8% of recipients without EAD (relative risk = 10.7). More recipients with EAD had graft failure (26.1%) than recipients with no EAD (3.5%) (relative risk = 7.4.). Table 10 reports the incidence in EAD in various liver transplant centers.

Table 10. Incidence of Early Allograft Dysfunction in USA Liver Transplant Centers

	Incidence of EAD		Comments
	HMP	control	
Guarrera's analysis[11] on EAD, 2010	5% (n=20)	25% (n=20)	Hypothermic machine perfusion (HMP)
Deschenes et al[8],1998		23% n= 710	Control
Olthoff, et al[10]. 2010.		23.2% (n=297)	Deceased donor liver transplants using cold storage. EAD was highly associated with graft loss and recipient mortality at 6 months. (9.1% graft loss rate died within 6 months (5.7% mortality rate).
David D Lee et.al.[7] 2016		26.5% (n=1950)	1-, 3-, and 5-year allograft and recipient survival for recipients who developed EAD were significantly inferior to those who did not
Jana Hudcova et. al. 2017[9]		36 % (n=239)	EAD was significantly associated with higher one-year graft loss. There was no difference in patient mortality between groups

Liver Transplant Risk Assessment Indices:

Donor risk index (DRI)

Donor characteristics significantly impact liver transplantation outcomes. However, the quantitative risk associated with combinations of characteristics are unclear. Using national data from 1998 to 2002, Feng et. al.[6] developed a quantitative DRI, including seven donor characteristics that independently predicted significantly increased risk of graft failure.

Donor age over 40 years (and particularly over 60 years), donation after cardiac death (DCD), and split/partial grafts were strongly associated with graft failure.

Marginal Livers (ML):

ML have been used to expand the donor pool. National utilization of MLs is variable, and in some centers, they are never used. The SRTR/OPTN 2011 registry identified risk factors for graft loss in first time recipients, who received a deceased donor liver: cold ischemia time, high serum sodium level, cause of donor death, gamma-glutamyl transferase (GGT) level, and female donor sex were predictors of graft loss at three months. In addition, CIT, GGT, and cause of donor death were associated with 12-month graft loss.

Marginal liver grafts[12] included those with any of the following characteristics:

- Liver donor age >70 years
- Livers discarded regionally and shared nationally
- Livers from hepatitis C positive donors
- Livers with CIT >12 hours
- Livers from DCD donors
- Livers with >30% steatosis
- Livers split between two recipients

The mortality rate for recipients, who were waitlisted at the transplant program using marginal liver grafts was lower compared with the national waitlist mortality rate (19 versus 24 percent).

Halazun et al.[13], performed a single center outcomes analysis of ML graft transplants performed from 1998 to 2016 and compared outcomes to standard criteria (SL) and living donor (LD) livers. ML grafts were defined as above. A total of 2050 liver transplant recipients were studied. Of these, 960 (46.8%) received ML grafts. Most ML were from organs turned down regionally and shared nationally (69%) or donors >70 years (22%). Their analysis indicated that recipient and graft survival of patients receiving ML grafts were comparable to those of patients receiving SL transplants.

DCD Donors:

The demand for liver transplantation exceeds the availability of grafts. Approximately 20% to 30% of recipients on the waiting list for liver transplantation die or are delisted for disease progression before they receive a transplant.[14,15,16] One possible strategy to increase the donor pool is the use of marginal grafts, such as steatotic grafts, grafts from older donors, or DCD livers. The percentage of DCD grafts in the OPTN data from 2009 to 2011 ranges from 0.2 to 11.4 across different programs in the USA.

Cold Storage is poorly tolerated by marginal livers and results in severe reperfusion injury and graft dysfunction[17] and DCD liver transplantation is associated with a high risk (20%-40% of cases) for ischemic-type bile duct injury.[18,19,20] This has resulted in strict selection criteria for DCD grafts, and as a result, they are often declined on the basis of donor age or warm and cold ischemia times.

According to the criteria for donor quality as per British Transplantation Society Guidelines[21] for DCD's, all optimal DCD Livers should be transplanted (age < 50, weight < 100 kg, functional warm ischemic time, (FWIT) < 20 min, CIT <8 hrs, steatosis < 15%, ICU Stay <5 days.) while Sub-optimal DCD livers (age >50 years, weight >100 kg, Intensive care stay >5 days, FWIT 20-30 minutes, Cold ischemia time >8 hours (up to 12 hours), Steatosis >15%), should be used selectively.

Interestingly, a retrospective trial of the United Network for Organ Sharing data compared graft survivals for recipients who received liver transplants from DBD donors of age ≥ 60 years, DBD donors < 60 years, and DCD donors < 50 years of age. Trial results showed that DCD livers of age < 50 years with < 6 hours of cold ischemic time had superior graft survival when compared to DBD livers ≥ age 60 years ($P < 0.001$).[22]

Post Reperfusion Syndrome (PRS):

Initially, PRS was based on mean arterial pressure (MAP). Later Hilmi et al. [23] expanded this definition introducing a classification of PRS as mild and severe:

(1) mild PRS, defined by a decrease of MAP and/or heart rate (HR) not reaching 30% of baseline value, lasting for less than 5 min, and responsive to an intravenous bolus dose of calcium chloride (1 g) and/or epinephrine (≤ 100 mcg) without the need to start a continuous infusion of vasopressors; and

(2) severe PRS, defined by greater hemodynamic instability, a drop in MAP/HR exceeding 30% of baseline, asystole or hemodynamically significant arrhythmias; or the need to start the infusion of vasopressors during the intraoperative period and to continue throughout the postoperative period.[22]

PRS incidence varies largely among studies, ranging from 12% to 77%. This variability could be the result of differences in the recipient population, definition, and standard pretreatment across transplant centers.[24] PRS definitions, severity, and the numerosity of possible confounding factors greatly complicates its interpretation.[25]

Biliary Complications:

Ischemic and non-ischemic biliary complications (IBCs) are a serious concern after liver transplantation and a routine cholangiography is usually performed between postoperative days 10-14. IBCs appear to be the result of the ischemia/reperfusion-induced tissue injury associated with the harvest and implantation of allografts.[26] These types of complications are not associated with biliary reconstruction, the primary liver disease, cytomegalovirus infection, allograft rejection or the presence of a positive lymphocytotoxic crossmatch.

Endothelial and biliary epithelial cells have been shown to be more vulnerable to ischemia/reperfusion injury than hepatocytes[27], and IBCs are strongly associated with the duration of cold ischemic storage of allografts in both Euro-Collins solution and University of Wisconsin solutions[28].

IBCs developed in approximately 9.6% of recipients at a mean of 23.6 ± 34.2 weeks post-transplantation (6 months) with a median time of 11.3 weeks (range 1.1 to 175 weeks). [29] The severity of IBCs presenting early (<1 year) after orthotopic liver transplantation (OLT) is generally associated with preservation-related risk factors. Cold and warm ischemia times are significantly longer in recipients with early IBCs compared with IBCs presenting late (>1 year) after OLT.[30] Only severe ischemic damage to the biliary structures will present early as IBCs, while more subtle damage may become apparent later in time. Therefore, differences in IBCs do not always become evident early after transplantation.

Buis et al., found that the median time from transplantation to diagnosis of IBCs was 4.1 months (range 0.3 to 155 months) with more than 50% of cases presenting in the first year after transplantation. Long-term follow-up showed that the number of grafts that develop IBCs continued to increase up to 12 months after transplantation with smaller increases beyond the first year up to ten years after transplantation. IBCs presentation within the first year after OLT were associated with preservation-related risk factors.[28]

6.2 PROTECT Trial

The OCS Liver PROTECT trial (b)(4) is the pivotal study in support of this PMA. The PMA also includes additional supporting evidence including the REVIVE trial, which was performed outside the U.S. (25 recipients) as well as eight compassionate use reports. The REVIVE trial was not intended to serve as a main dataset for the support of this PMA and is not included in this executive summary due to limitations in the data provided (the trial had no control arm, no protocol was provided, and only a brief

summary of clinical results was included in this PMA); therefore, the REVIVE study does not substantially contribute to our assessment of the performance of the device. The compassionate use cases were not included in this PMA, because in these cases, the OCS Liver System was used for multi-organ transplants conducted at one institute under one investigator.

The PROTECT trial was designed as a prospective, multi-center, open-label, randomized trial of 300 transplant recipients from 20 US transplant sites randomized 1:1 to the OCS Liver or Control. The Control was the standard of care, which is cold, static storage. The first in-human, staged trial began on January 24, 2016. Part A of the trial was for 20 recipients. Part B was approved for the remaining 280 recipients on November 16, 2016. The trial closed to recipient enrollment on October 15, 2019. Thirty-day follow-up was completed on November 19, 2019; the last 6-month follow-up was on March 28, 2020. The last 12-month follow-up was on October 15, 2020. October 15, 2020 is the cut-off date for the data provided in this PMA.

Recipients were followed for a minimum of 30 days post liver transplant. Recipients will be followed for a maximum of 24 months post-transplant. The following data were collected at 6 and 12 months: Recipient and graft survival; incidence of ischemic biliary complications and method of diagnosis; liver graft-related SAEs at 6 months only; and liver graft-related re-hospitalizations after initial discharge, along with the primary reason/diagnosis for the hospitalization and the length of stay.

6.3 PROTECT Trial Objective

The PROTECT trial was conducted to compare the safety and effectiveness of the OCS™ Liver (OCS) vs. standard cold storage (Control) to preserve and assess donor Livers having one or more of the following characteristics:

- Donor age ≥40 years old; or
- Expected cross clamp time ≥6 hours; or
- Donor after circulatory death (DCD) with age ≤55 years old; or
- Steatotic liver >0% and ≤40% macrosteatosis at time of retrieval (on pre-retrieval histology).

6.4 PROTECT Trial Design

6.4.1 Randomization

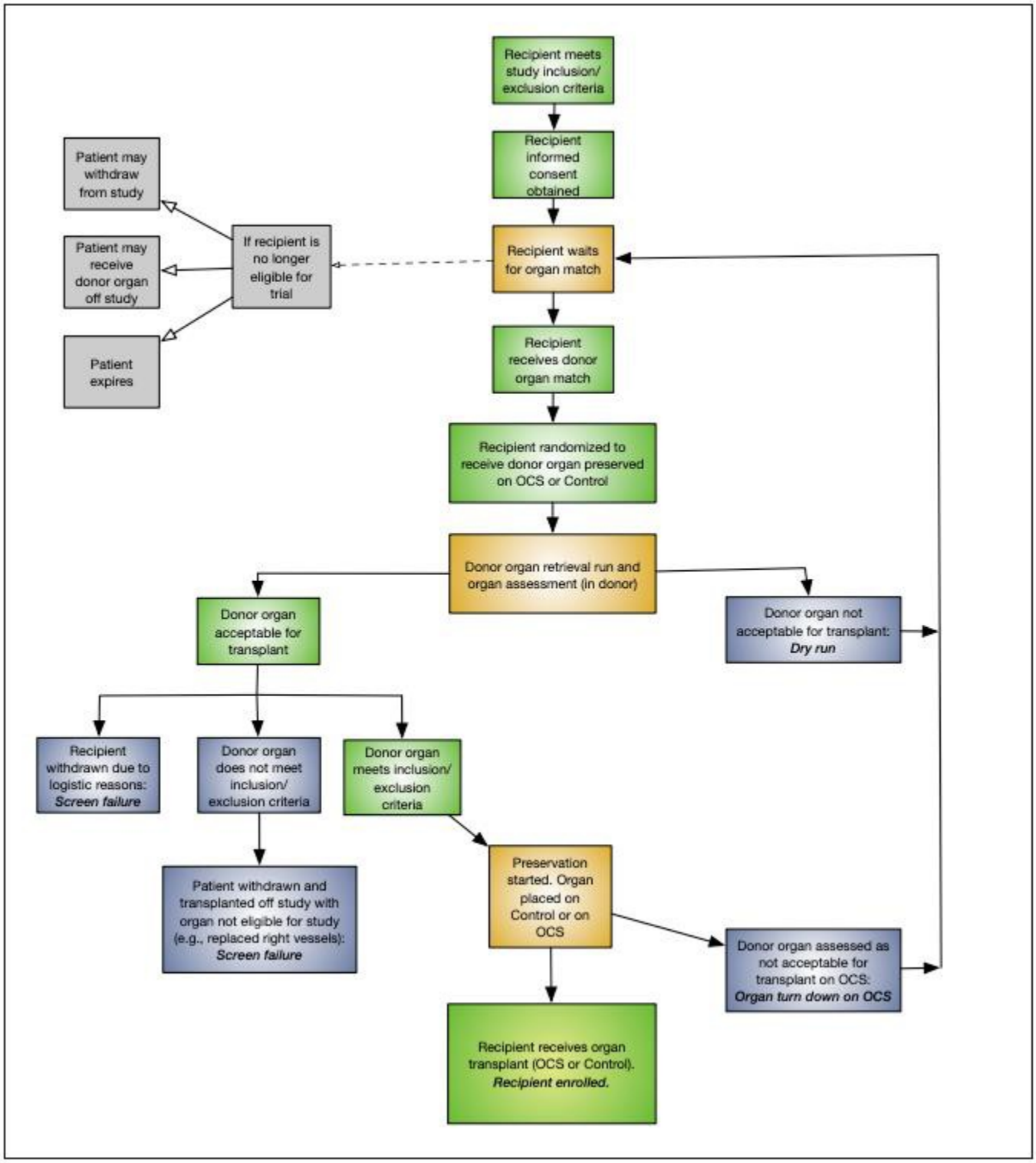
After confirmation of eligibility, obtaining informed consent, and identifying a matching donor liver, potential liver transplant recipients were randomized 1:1, and donor livers were preserved using either the OCS Liver System or the standard cold storage preservation technique. In some cases, donor organs were found to be unacceptable for transplant. In these cases, the recipients who had been randomized to those donor organs were considered “dry run” recipients. The “dry run” recipients were not transplanted with the matching donor liver, and were put back on the waiting list for an organ match and treated as a new recipient (i.e., they were re-randomized if they were matched again).

No stratified randomization was planned for DBD and DCD recipients.

The sponsor states in their clinical summary report that randomized trials in the field of organ preservation for transplantation are complex due to the multi-factorial and complex nature of the organ allocation and retrieval process. The sponsor selected a trial design that included randomization of recipients prior to donor liver retrieval and re-randomization when the recipient did not receive the matched donor liver.

The Agency recommended revision of the randomization process in the second stage of the trial (11/16/2016), so that the randomization assignments were revealed to the retrieval team after confirmation of donor organ eligibility upon final assessment. However, throughout the PROTECT trial, the candidate recipients were randomized instead of the donor livers. As a consequence, the transplant team, including the procurement surgeon, knew the treatment (method of preservation) assignments before the donor surgery started, which could introduce bias in the decision whether the liver is acceptable for transplantation and/or suitable for the OCS system. Multiple screening failures, "dry runs," and re-randomization of the already randomized recipients are shown in Figure 14 below which presents a schematic of the PROTECT trial course.

Figure 14. PROTECT Trial Course



6.4.2 Inclusion and Exclusion Criteria

Separate inclusion and exclusion criteria were used for prospective donor organs and consented recipients.

Recipient Eligibility Criteria

Recipients were screened for eligibility on two occasions: at the time of consent and again on the day of planned transplantation.

Inclusion

- 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

Exclusion

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

Donor Liver Eligibility Criteria

Inclusion

- 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)).

Exclusion

- 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

Acceptability of the donor organ was also based on the judgement of the procurement surgeon. Reasons for organ unsuitability include excessive macrosteatosis, vascular anomalies, failure to expire of the DCD donor.

6.4.3 Trial Endpoints, Hypotheses, and Planned Analyses

6.4.3.1 Primary Effectiveness Endpoint: The Incidence of Early Liver Allograft Dysfunction (EAD) Within the First 7 Postoperative Days

The Incidence of Early liver Allograft Dysfunction (EAD) or primary non-function, is defined in this study 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 protocol specified the primary effectiveness endpoint of EAD is loosely based on the 2010 Olthoff publication[10], 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.

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 first 7 postoperative days for the OCS and Control, respectively, and δ is the noninferiority margin, which is here taken to be 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 will be tested for superiority, using Fisher's exact test with a two-sided alpha of 0.05.

The sample size for this trial was determined based on the primary effectiveness endpoint, assuming a one-sided, normal approximation test for non-inferiority, an alpha level of 0.05, a non-inferiority margin of 0.075, a 1:1 allocation, true proportions for the primary effectiveness endpoint of 0.2 for the OCS treatment and 0.25 for the Control treatment, and power of 80%. Based on these specifications, the

required sample size was determined to be 144 transplanted recipients per treatment group, or 288 total transplanted recipients. To ensure an adequate number of recipients in the Per Protocol Population, the sample size was increased to a total of 300 transplanted recipients. Recipients will be enrolled until there are either 290 recipients in the Per Protocol Population or a total of 300 transplanted recipients, whichever comes first.

6.4.4.2 Secondary Effectiveness Endpoint: OCS Donor Liver Assessment

OCS donor liver assessment during perfusion is defined as, among donor livers preserved using OCS for the entire preservation period, the proportion of livers on which measurements of all of the following during perfusion were available on OCS device before transplant:

- Lactate level (every two hours ± 20 mins. of time window)
- Average bile production rate (based on total bile production volume and duration of OCS perfusion)
- Hepatic Artery Pressure (continuously averaged every 30 minutes)
- Portal Vein Pressure (continuously averaged every 30 minutes)

The objective for this secondary endpoint is to show the proportion of donor livers preserved using OCS for the entire preservation period with all the required measurements available is above the performance goal of 85%. The null and alternative hypotheses for the OCS donor liver assessment during perfusion endpoints are:

$$H_0: \pi_3 \leq 0.85$$
$$H_1: \pi_3 > 0.85$$

Where π_3 is the true proportion of livers, among donor livers preserved using OCS for the entire preservation period, on which measurements of lactate level, average bile production rate, Hepatic Artery Pressure and Portal Vein Pressure during perfusion were available on the OCS device before transplant. The hypothesis test was planned to be evaluated with a one-sided alpha = 0.05 using exact test. If information for any of the four measurements is missing, the donor liver was planned to be classified as not meeting the OCS donor liver assessment criteria.

FDA Comment: Perfusion parameter measurements were prespecified and included predefined target values, cut-off values, and trends. However, there were no predefined viability criteria. For example, criteria for viability[31] of bile production could have been predefined as cumulative bile production ≥30 g in 6 hours. The Agency believes that lactate is an especially important measurement to validate and prespecify the viability criteria.

6.4.4.3 Secondary Effectiveness Endpoint: Recipient Survival at Day 30 Post-transplantation

The objective for this secondary effectiveness endpoint is to show OCS is non-inferior to Control in terms of proportion of recipients surviving to Day 30 post-transplantation with a non-inferiority margin

of 7.5%. The statistical hypotheses for this secondary effectiveness endpoint, recipient survival at Day 30 post-transplantation, are as follows:

$$H_{20}: \pi_{2,OCS} \leq \pi_{2,Control} - \delta,$$
$$H_{21}: \pi_{2,OCS} > \pi_{2,Control} - \delta,$$

where $\pi_{2,OCS}$ and $\pi_{2,Control}$ are the true proportions of recipients surviving to Day 30 post-transplantation for the OCS and standard of care treatments, respectively, and $\delta = 0.075$ is the noninferiority margin. The hypothesis was planned to be evaluated based on the Farrington and Manning score statistic with one-sided alpha of 0.05.

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

6.4.4.4 Secondary Effectiveness Endpoint: Recipient Survival at Initial Hospital Discharge Post Liver Transplantation

This secondary effectiveness endpoint, recipient survival at initial hospital discharge post liver transplantation, is analyzed in a manner analogous to the secondary effectiveness as recipient survival at Day 30 post-transplantation endpoint with the same non-inferiority margin of 0.075.

6.4.4.5 Safety Endpoint: Frequency of Liver Graft-related Serious Adverse Events (LGRSAEs) up to the 30-day Follow-up After Transplantation.

Safety is analyzed principally by examination of the frequency of liver graft-related serious adverse events (LGRSAEs) up to the 30-day follow-up after transplantation. This endpoint is defined as the number of LGRSAEs through 30 days post-liver transplantation per recipient, consisting of the following serious adverse events (at most one per type per person):

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

For the number of LGRSAEs, the objective is to show OCS is non-inferior to the Control with a non-inferiority margin of 1 in mean numbers of LGRSAEs up to the 30-day follow-up after transplantation. The statistical hypotheses are as follows:

$$H_{30}: \mu_{OCS} \geq \mu_{Control} + \delta,$$
$$H_{31}: \mu_{OCS} < \mu_{Control} + \delta,$$

where μ_{OCS} and $\mu_{Control}$ are the true mean numbers of LGRSAEs up to the 30-day follow-up after

transplantation per recipient with the OCS and standard of care treatments, respectively, and δ is the non-inferiority margin, which is 1.0. The safety endpoint was planned to be analyzed using a two-sample t-test with a one-sided alpha level of 0.05.

If non-inferiority is demonstrated, the results will be tested for superiority, using a two-sample t-test with a two-sided alpha of 0.05.

Survival and Graft Survival

At the time of IDE approval, the Agency informed the sponsor that according to the European Liver Transplant Registry (ELTR) data on 39,196 liver transplant recipients, a significant portion of recipient deaths, re-transplantations, and serious adverse events occurred after 30-days post-transplantation.[32] FDA recommended that the sponsor include recipient and graft survival at 1 year post-transplantation as secondary effectiveness endpoints and incidence of LGRSAEs within 6 months post-transplantation as safety endpoints.

The sponsor revised their protocol to collect recipient and graft survival at 6, 12 and 24 months, but did not include these as secondary effectiveness endpoints, and did not define the graft survival in the protocol. The sponsor also revised their protocol to include 6-month LGRSAE post-transplantation. The sponsor reasoned that endpoints obtained after 30 days would be confounded by non-preservation related factors. The Agency believes that sufficient trial randomization would account for confounding factors. Therefore, FDA recommended that recipient and graft survival as well as LGRSAEs beyond 30 days post-transplant, were relevant secondary effectiveness endpoints, and secondary effectiveness and safety endpoints should not be limited only to 30-days post-transplantation.

Other Clinical Endpoints

The trial protocol also specified collection of data for the following clinical endpoints:

- Length of initial post-transplant intensive care unit (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 over the following timepoints:
    - During anhepatic phase immediately before reperfusion of the transplanted liver
    - 30-40 minutes after hepatic artery and portal vein reperfusion of the transplanted liver
    - 90-120 minutes after reperfusion of the transplanted liver
- Pathology sample score for liver tissue samples taken at the following timepoints (applies to both OCS and Control arms):
    - Donor liver pre-retrieval
    - Post-OCS and Control preservation at the end of back preparation and immediately before the start of re-implantation
    - Post reperfusion 90-120 minutes after reperfusion of the transplanted liver (prior to abdominal closure)

6.4.5 Analysis Populations

The following analysis populations were defined in the protocol. As discussed below, FDA has some concerns with the definitions of study populations, and the selection of the population for various endpoints.

Per Protocol Population

The Per Protocol (PP) Population consists of all randomized recipients who are transplanted and have no major protocol violations and for whom the donor liver received the complete preservation procedure as per the randomization assignment. The major protocol violations that exclude a recipient from this population are the following:

- Ineligible for the study according to the recipient inclusion and exclusion criteria
- Ineligible for the study according to the donor organ inclusion and exclusion criteria
- Recipient is transplanted with a liver with preservation other than that to which the recipient was randomized
- Failure to complete adequate post-transplant assessments to support the primary, secondary or safety endpoints
- Other major protocol violations

The final designation of major protocol violations resulting in an exclusion from the PP Population were made during a blinded review by the Clinical Events Committee (CEC) prior to database lock.

Modified Intent-to-treat Population

The Modified Intent-to-Treat Population (mITT) consists of all randomized recipients who are transplanted in the PROTECT trial. In analyses based on mITT Population, recipients are analyzed as randomized. The protocol indicates that the mITT Population analyses is the secondary analyses of effectiveness.

As Treated Population

The As Treated Population (AT) consists of all treated recipients, i.e., all recipients who are transplanted in the study with a donor liver preserved with either OCS or Control. In analyses based on this population, recipients are analyzed as treated. A recipient who receives a liver with some preservation with OCS and some with standard of care is classified as OCS, because any donor liver preserved with OCS at any time during the preservation process is classified as OCS. Analyses of safety endpoints is performed based on the AT Population.

Donor Liver Population

The Donor Liver Population consists of all donor livers for which the potential recipient was randomized, and which have preservation initiated using OCS or Control in the PROTECT trial. A liver with some preservation with OCS and some with standard of care is analyzed as preserved with OCS.

Modified Intent-to-treat 2 Population

The Modified Intent-to-Treat 2 Population (mITT2) consists of all randomized recipients who are transplanted in either the PROTECT trial or outside of the PROTECT trial. In analyses based on the mITT2 Population, recipients are analyzed as randomized.

Intent-to-treat Population

The Intent-to-Treat Population (ITT) consists of recipients who have signed informed consent, been enrolled in the study, randomized, and the assigned liver preservation method has been initiated. In analyses based on the ITT Population, recipients are analyzed as randomized.

The protocol specified that the primary endpoint and secondary survival endpoints would be evaluated in the Per Protocol population.

The secondary effectiveness endpoint – OCS donor liver assessment was planned to be analyzed using the Donor Liver Population but limited to livers preserved with OCS for the entire preservation period.

The safety endpoint – number of liver graft-related SAE was planned to be analyzed based on the As Treated Population.

6.4.6 Handling Dropouts and Missing Data

Multiple imputation (MI) methods were planned to be used for recipients with missing outcomes for the primary effectiveness endpoint and for the secondary effectiveness endpoints of recipient survival at Day 30 post-transplantation and recipient survival at initial hospital discharge post liver transplantation.

The following covariates are used to impute missing data outcomes:

- Donor after cardiac death (DCD donor): (Yes, No)
- Donor age: (< 40 years, ≥40 years)
- Steatotic liver: (≤ 20% macrosteatosis at time of retrieval, > 20% macrosteatosis at the time of retrieval).
- Recipient gender: (Male, Female)
- Recipient age

A tipping point sensitivity analysis based on the Per Protocol Population was planned to be used to assess the effect of missing data.

6.4.7 Multiplicity Adjustment

Fixed sequential testing for non-inferiority was planned for the primary and secondary effectiveness endpoints. The fixed sequence testing is shown below. Similarly, testing superiority for these endpoints followed the same sequence.

1. Primary Effectiveness Endpoint
2. OCS donor liver Assessment
3. Recipient Survival at Day 30 Post transplantation
4. Recipient Survival at Initial Hospital Discharge Post Liver Transplantation

FDA Comment: The sponsor did not clearly state whether both non-inferiority and superiority need to be demonstrated in order to test the next endpoint in the sequence. It appears that non-inferiority and superiority will be tested in two parallel sequences in the sponsor's proposed fixed testing sequence, and the sequence did not account for the safety endpoint. As such, the study overall type I error is not controlled at a one-sided alpha of 0.05. This was the subject of an IDE Study Design Consideration; however, the sponsor has not addressed FDA's concern.

6.4.8 Subgroup Analysis

Subgroup analyses of the primary effectiveness endpoint and the secondary effectiveness endpoints was planned for the following subgroups of recipients:

- DCD recipients (Yes/No)
- Fatty liver recipients (Macrosteatosis: ≤ 20%, >20%)
- Donor Age (≤ 50 years old, > 50 years old)
- Recipient MELD score (≤ 25, >25)
- Donor organ total cross-clamp time < 6 hours, ≥ 6 hours (DBD donors only)
- Donor Inclusion Criteria (each criterion separately, one criterion, multiple criteria)

No data imputation or statistical tests was performed for the subgroup analyses for the effectiveness endpoints. Additional subgroup analyses were performed for selected demographic and baseline comparisons (recipient and donor) and for adverse events (recipient).

6.4.9 Pooling by Recipient Investigational Site

The primary effectiveness endpoint was planned to be evaluated pooling by recipient investigational site and its analysis was planned to be performed on observed data on the mITT and PP populations. The significance level for the test of the interaction of treatment by pooled site will be a=0.15.

A pooled site variable will be created in order to pool small sites geographically. The five investigational sites with the highest number of transplanted recipients will not be pooled. The remaining sites will be pooled by U.S. geographic region (Northeast, South, and West). The pooled sites by geographic region will have a minimum of 20 transplanted recipients.

6.5 PROTECT Trial Results

6.5.1 Recipient and Donor Liver Disposition

As seen in Figure 15, there were 476 unique matched donor livers, of which 176 donor livers were not

accepted in the PROTECT trial.

- 130 of these livers were rejected for transplant in the donor body after randomization. The reasons for nonacceptance of these 130 donor livers were
    - the DCD donor did not expire within 30 minutes (47)
    - clinical judgement at retrieval (31)
    - cirrhosis or fibrosis (9)
    - vascular abnormalities or diseased (4)
    - donor-recipient mismatch (3)
    - liver or kidney malignancy discovery during retrieval (2)
    - other logistical reasons (12).

- Three of the livers were turned down after assessment on the OCS device due to reasons of high lactate and bridging fibrosis reported on pre-retrieval biopsy.

- 43 of these organs were transplanted to 43 consented recipients off study using cold storage (Control) (OCS=28, Control=15) due to
    - liver abnormalities such as the presence of accessory vessels (39)
    - logistical reasons (4).

The Agency is concerned that more donor livers withdrawn and transplanted off study using cold storage occurred in the OCS arm (28) compared to the Control arm (15).

Among 429 consented recipients, 428 recipients were randomized. One recipient was not randomized, but was treated with a donor liver preserved using OCS. Among 429 consented recipients, 300 recipients were considered enrolled in the PROTECT trial, and the other 129 recipients were not considered enrolled in the PROTECT trial by the sponsor.

Among those 129 recipients who were not considered enrolled in the study,

- 43 recipients were transplanted off PROTECT trial using cold storage (Control) due to donor liver screen failures

- 86 recipients were pooled in a "dry-run" category defined by the sponsor as recipients who were initially randomized but then later their matched donor livers were not accepted for transplantation, and thus they did not have a chance to have re-randomization for the next available matched donor liver. Among those 86 "dry-run" recipients,
    - 49 recipients were transplanted off PROTECT trial
    - 4 died while on the waiting list
    - 2 withdrew consent
    - 9 delisted
    - 22 remained on the waiting list at the end of the study.

The sponsor's ITT population in the clinical report included 343 recipients (300 plus 43 who were transplanted off study with cold storage livers (Control)) instead of 428 randomized recipients (the all

randomized subject population that is typically used as the Intention-to-Treat analysis population for randomized controlled trials). Furthermore, in Figure 16, the sponsor's mITT population only included 298 recipients who were randomized and transplanted in the PROTECT trial instead of 392 randomized and transplanted recipients (343 recipients in the sponsor's ITT population plus 49 recipients in the dry-run cohort who were transplanted off PROTECT trial using Control).

A higher rate of screening failures (SF) in the OCS arm was initially observed during the Part A (the first 20 recipients), of the PROTECT trial and continued through the Part B of the trial (the rest of the 300 recipients). In a report dated November 23, 2017 the sponsor stated 38% of the first 66 randomized recipients resulted in screening failures. Most of the reported screening failures (72%, 18 out a total 25 SF) were observed in the OCS arm. The sponsor changed their categorization of screening failure, which was originally a consented recipient matched with randomized donor liver which eventually is not transplanted and allowed screening failure recipients that returned to the waiting list for re-randomization to not be considered screening failures. The Agency believes that these cases should be considered screening failures, regardless of whether they return to the waiting list and are re-randomized or they are subsequently withdrawn and transplanted out of the trial.

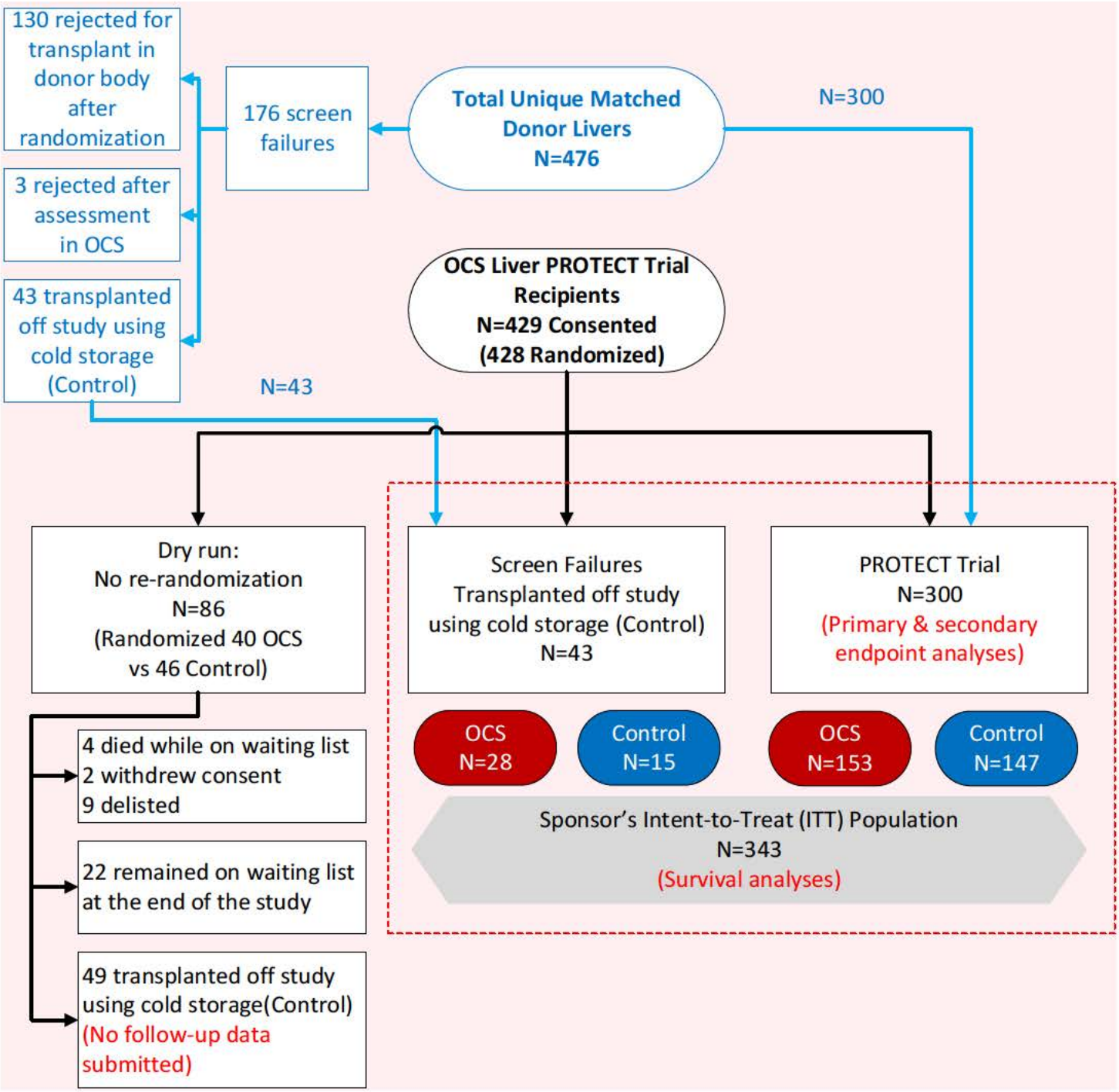
The sponsor associated this early imbalance on lack of attention of the trial investigators to accessory vessels in the control livers. They conducted a retrospective revision of operative reports in which five cases were found to have accessory vessels in the control arm. These cases were considered screening failures by the sponsor. In the final trial report, all screening failures (n=176) were distributed evenly, OCS=88 and Control=88. However, screening failures due to recipients withdrawn and transplanted out of the trial after randomization using control were more frequently observed in those randomized to OCS=28 compared to those randomized to Control=15.

As stated in 4.2 PROTECT Trial Design Considerations (SDC), the Agency considers that early randomization increased the complexities in data interpretation. For further details on the Screening failures and dry run, please refer to Appendix 1.

Figures 15 and 16 illustrate the analysis populations used by the sponsor. As shown in Figure 15, the sponsor defined ITT population consists of 343 (80%) of the 428 randomized recipients. The 6, 12, and 24 months survival analyses are based on this population. Except for these survival data, the primary, secondary, and most other endpoint data are available only for the sponsor's mITT and PP populations, which are 70% (298/428) and 68% (293/428) of all randomized recipients (Figure 16). Figure 16 also shows the PP and AT population, both are close to the mITT population.

The "dry run" subjects (20%, 86/428) are excluded from the sponsor's ITT analyses. For a randomized trial, the Agency considers that the analyses based on all randomized subjects (true ITT) would give an unbiased estimate of treatment effect. Due to the high proportion of post-randomization exclusion in this trial, bias could have been introduced in the procedure and analyses if the reasons for exclusion were related to the treatment assignment.

Figure 15. Recipient and Donor Liver Disposition



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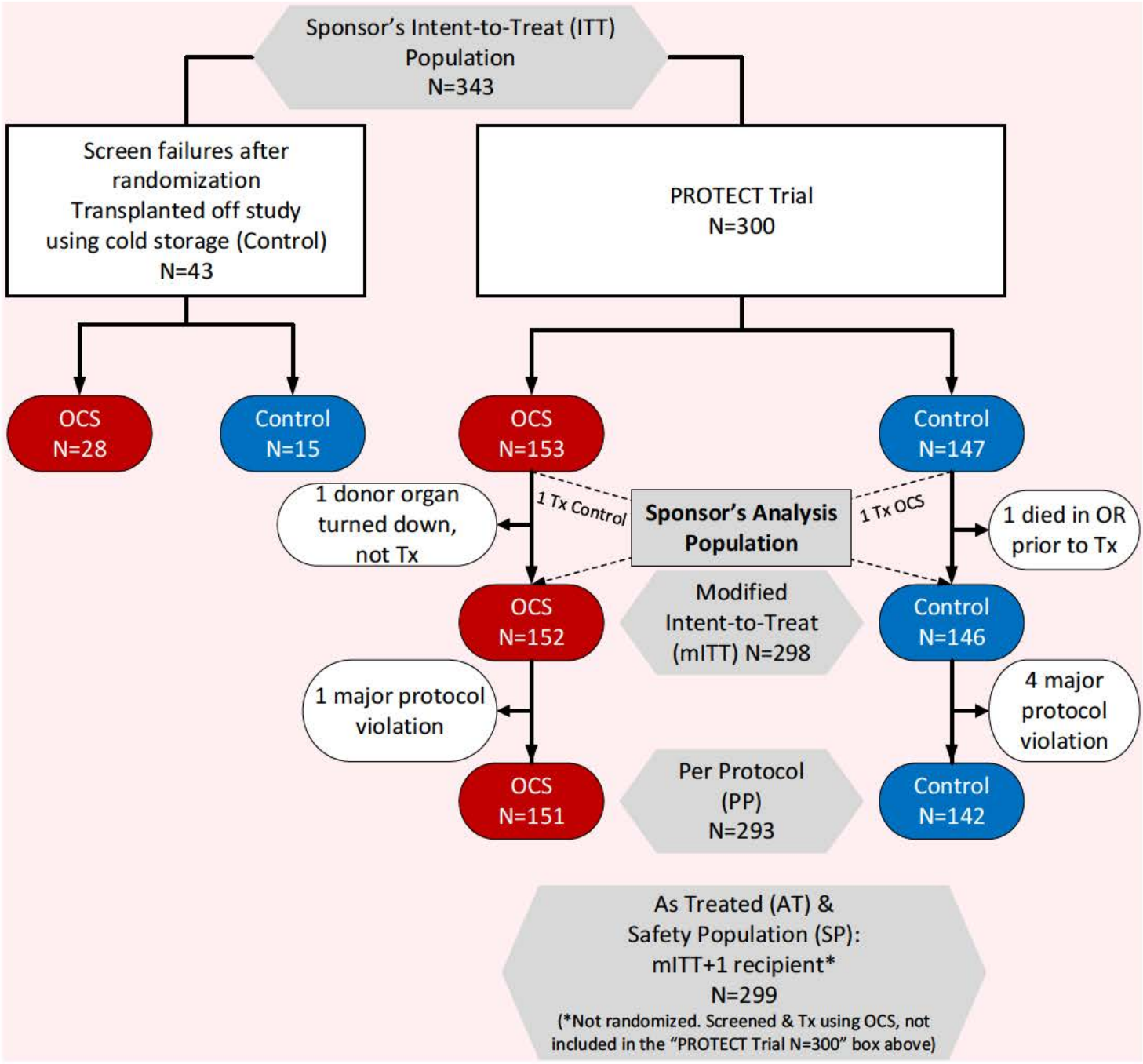
Source: the sponsor's Figure 2, Table 4 in the Appendix 6 of 003_App 0-1 - OCS Liver PROTECT CSR with Apps - 2.9.21v2.pdf, the sponsor's Figure 1 of the sponsor's response to interactive review request in 7/20/20 Email, and the submitted dataset "ADSL" in the amendment.

Figure 16. Recipient Disposition and the Sponsor's Analysis Populations



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Re-randomization

The panel will be asked to discuss how interpretation of study results is impacted by the rate of screen failures among the donor livers, and the size of the "dry run" category among the recipients.

Recipients who were not transplanted with the matching donor livers ("dry run recipients")were put back on the waiting list for another round of randomization and organ match and treated as a new candidate recipient who had no previous randomization who had no random assignment (i.e., were re-randomized if they were matched again). As such, 11% (38/343) of recipients had at least 2 randomizations. Frequencies of re-randomization are displayed in the following table:

Population	OCS				Control			
	Number of Randomizations							
	1	2	3	≥ 4	1	2	3	≥ 4
mITT % (n/N)	89.5 (136/152)	8.6 (13/152)	1.3 (2/152)	0.7 (1/152)	87.7 (128/146)	11.6 (17/146)	0.7 (1/146)	0.0 (0/146)
ITT % (n/N)	89.5 (162/181)	8.3 (15/181)	1.1 (2/181)	1.1 (2/181)	88.3 (143/162)	11.1 (18/162)	0.6 (1/162)	0.0 (0/162)

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Source: the sponsor's submitted dataset "ADSL" in the amendment

6.5.2 Demographics and Characteristics

Tables 11 and 12 below report the recipient and donor demographic and baseline characteristics of the PROTECT trial.

Table 11. Recipient Demographic and Baseline Characteristics (AT population=299)

Parameter	OCS (N=152)	Control (N=146)
Recipient Age (yrs): mean ± SD (Min-Max)	57.07 ± 10.33 (19.5 - 76.6)	58.59 ± 10.04 (20.8 – 77.8)
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
(Min-Max)	(16.3 - 45.5)	(17.1 - 44.7)
MELD Score: mean ± SD	28.4 ± 6.90	28.0 ± 5.71
Median (Min - Max)	29.0 (6 - 49)	29.0 (9 - 46)
Recipient Baseline Characteristics		
History of diabetes	44 (28.8%)	44 (30.1%)
History of liver cancer	60 (39.2%)	63 (43.2%)
Primary diagnosis		
Cholestatic Diseases	9 (5.9%)	8 (5.5%)

Chronic Hepatitis	27 (17.6%)	36 (24.7%)
Alcoholic Cirrhosis	54 (35.3%)	48 (32.9%)
Metabolic Diseases	6 (3.9%)	6 (4.1%)
Primary Hepatic Tumors	14 (9.2%)	15 (10.3%)
NASH	24 (15.7%)	20 (13.7%)
Other	19 (12.4%)	13 (8.9%)

The majority of the recipients were males (66-69%), 57-58 years of age, with a mean MELD score of 28. The most prevalent primary diagnosis was alcoholic cirrhosis. Demographic and baseline characteristics (AT, mITT, PP and ITT populations) did not show clinically significant differences. Mean and median MELD scores in the AT population are similar across the OCS and CS groups, 28.4 and 28 respectively. The reported 3-month mortality for MELD score 28, in the Wiesner et al. 2003 OPTN registry analysis[2] is 19.6%. .

Table 12 Donor Demographic and Baseline Characteristics (AT population=298*)

Parameter	OCS (N=152)	Control (N=146)
Donor Age (yrs): 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%)
Donor Characteristics (1)		
≥ 40 years old	102 (67.1%)	93 (63.7%)
Total cross clamp ≥ 6 hours	48 (31.6%)	56 (38.4%)
DCD ≤ 55 years old	28 (18.4%)	13 (8.9%)
Steatotic liver > 0% and ≤ 40% macrosteatosis at time of retrieval	95 (62.5%)	86 (58.9%)
Multiple Donor Characteristics	95 (62.5%)	85 (58.2%)

*: Does not include donor organ for recipient (b)(4) , as this recipient was not randomized.
(1) Multiple donor characteristics (inclusion criteria) could be met (total 60.4% of all donors).

Donor Demographic and Baseline Characteristics (in AT population, excluding the donor organ for

recipient (b)(4) , mITT, ITT and PP populations) showed similar mean donor age and cause of death across OCS and Control arms. Both donor groups were similar for risk factors: Age ≥ 40 years, cross clamp time > 6 hours and macrosteatosis ≤ 40. Donors were young individuals, mean age was 46 – 47 years old across arms.

Both donor groups were similar in risk factors of age ≥ 40 years, cross clamp time > 6 hours and macrosteatosis.

The OCS arm included significantly more DCD with age ≤ 55 years donors compared to the Control; 28/152 (18%) versus 13/146 (9%), respectively. As discussed previously, there was no stratified randomization of the DCD and DBD populations. Note: This was an open-label trial in which the investigators knew which organ would go on which arm prior to matching with a recipient.

The information on donor characteristics and preservation data is limited, so FDA cannot perform an appropriate assessment on imbalances across trial arms and outcomes. This information is important for the characterization of the population included in this trial.

In order to better understand the quality of the DCD organs in the PROTECT trial, we compared the information provided for the DCD donor organ characteristics from the sponsor to criteria established for Optimal and Suboptimal DCD organs by the British Transplant Society[21]. Note that to be considered an optimal DCD organ, a liver must meet all the criteria defined by the first column of Table 13 below. Criteria for suboptimal, but selectively transplantable, are shown in column two of Table 13 below.

Table 13. DCD Donor Demographic and Baseline Characteristics (AT population) in PROTECT trial compared to British Transplant Society Criteria for Transplantable DCD Livers

Criteria for donor quality as per British Transplantation Society Guidelines for DCD's[21]		**PROTECT Study Post- Hoc Subgroup Analysis in DCD**		
Optimal DCD (Transplantable)	**Suboptimal (Transplantable - use selectively)**	**Risk Factors**	**OCS-DCD 28 /152 (18.4%)**	**Control-DCD 13/146 (8.9%)**
Donor age < 50	Donor age >50	Donor age < 50	23 (82%)	12 (92%)
FWIT < 20	FWIT 20-30 min	WIT 20-30	18 (72%)[1]	7 (58.3%)[2]
CIT < 8 hrs	CIT 8-12 hrs[3]	CIT 8-12 hrs[3]	8 (28.6%)	0 (0%)
Macrosteatosis < 10 %	Macrosteatosis > 15%	Macrosteatosis < 15%	25 (100%)	10 (91%)[4]
Wt < 100 kg	Wt > 100 kg	Wt < 100 kg	21 (75%)	9 (69.2%)
Donor ICU stay < 5 days	Donor ICU stay > 5 days	-	-	-

DRI < 1.6	DRI > 1.6	-	-	-
(1) WIT not available for 3 OCS livers (2) WIT not available for 1 SOC liver (3) Total cross clamp time used for OCS, CIT (4) Data not available for N=2 SOC livers				

According to the table above the organs used in the PROTECT trial appear to fall in between the British Transplantation Society's Optimal and Suboptimal criteria[21].

FDA Comment: The DCD livers included in the PROTECT trial were of reasonable quality and adequate for transplantation.

The panel will be asked whether the study supports an indication for use that includes DCD livers.

6.5.3 Primary Effectiveness Endpoint Results

As seen in Table 14, the primary effectiveness endpoint of EAD at 7 days post-transplant was met under completer-case analysis in both mITT and PP populations: both non-inferiority and superiority can be established for the OCS arm compared to the Control arm. The use of OCS was associated with a statistically significant reduction of EAD compared to Control in the mITT population (OCS 17.9% vs. Control 32.4% with p=0.0047), and in the PP population (OCS 18.0% vs. Control 31.2% with p=0.0096). Since mITT and PP populations had only two recipients with missing EAD information, the conclusion remains the same under multiple imputation analysis which considers these 2 recipients with missing EAD information.

Table 14. OCS Liver PROTECT Trial Primary Effectiveness Endpoint - Incidence of Post-Transplant Early Allograft Dysfunction: mITT (N=298) and PP (N=293) Populations

Population (Completers)	OCS Treatment % (n/N)	Control % (n/N)	%Difference (2-sided 90% UCB) (OCS-Control)	P-value*	P-value**
				Non-inferiority Margin=0.075	Superiority
mITT	17.9 (27/151)	32.4 (47/145)	-14.5 (-6.2)	<0.0001	0.0047
PP	18.0 (27/150)	31.2 (44/141)	-13.2 (-4.9)	<0.0001	0.0096

* 90% two-sided upper confidence bound based on the Farrington and Manning score statistic., p-value based on the 90% two-sided Farrington and Manning score statistic. The non-inferiority margin is set to 7.5%. P-value associated with non-inferiority testing.

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

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Source: the sponsor's submitted dataset "ADSL" in the amendment

As stated in section 6.4.3.1, the sponsor's proposed definition of EAD did not include ALT, and as the Agency requested, the sponsor submitted a dataset with ALT information. Additional analyses were performed based on the full EAD definition, and both non-inferiority and superiority of the OCS arm

compared to the control arm are demonstrated in these analyses.

The statistical robustness of the EAD endpoint results can be confirmed using a tipping point analysis and multiple imputation method.

Components of EAD

Since the primary effectiveness endpoint EAD is a composite endpoint, each of the individual components of EAD (AST, bilirubin and INR) was evaluated separately to see whether EAD incidence is driven by one component and to ensure the similar trending across each component. Table 15 shows the number of recipients who met each of the 7 possible combinations of the three EAD components.

Table 15. 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

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Source: the sponsor's submitted dataset "ADSL" in the amendment

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). The larger number of recipients having EAD in the Control arm (47 versus 27, difference of 20, from the Total row) is almost fully driven by the larger number of recipients having AST in the Control arm (36 versus 17, difference of 19, from row 3). The numbers of recipients with INR only or bilirubin only (rows 1 and 2) are much smaller. The numbers of EAD events driven by bilirubin is lower in control arm (2) compared to the OCS arm (4).

Of the three criteria, AST is the least specific criterion, because it measures any injury to the liver, including anesthetics, drugs and other factors, in addition to reperfusion injury and recovery from such an event. Bilirubin level and INR at 7 days assess the transplanted liver's metabolic and synthetic function, both of which are much more relevant to EAD. Bilirubin level is determined by hepatocyte function, sinusoidal cell function and cholangiocyte function, the basic cell lines in the liver.

Table 16 shows the percentage of EAD events from each component in the PROTECT trial and in other

studies. In the PROTECT trial, most EAD events (72%) are driven by AST only (63% in OCS and 77% in Control), which is substantially higher than seen in other trials (36% in Hudcova[9] and 23% in Olthoff[10]). In other trials, more grafts met the EAD definition based on increased bilirubin at day 7 (53% in Hudcova[9] and 41% in Olthoff[10]).

The panel will be asked to discuss the significance of the results for the primary effectiveness endpoint.

	OCS	Control	control	control 010[10]
Incidence of EAD	27/151 (17.9%)	47/145 (32%)	86/239 (36%)	69/300 (23%)
1.- AST >2000 IU/L Within 7d (AST or ALT >2000 IU/L Within 7d)	17/27 (63%)	36/47 (77%)	22/86 (26%)	26/69 (38%)
2.- Total Bilirubin≥10 mg/dL on POD7	4/27 (15%)	2/47 (4%)	46/86 (53%)	28/69 (41%)
3.- INR≥ 1.6 on POD7	3/27 (11%)	2/47 (4%)	2/86 (2%)	5/69 (7%)
% with 1 component	24/27 (89%)	40/47 (85%)	70/86 (81%)	59/69 (86%)
% with 2 components	1/27 (4%)	5/47 (11%)	14/86 (16%)	6/69 (9 %)
% with 3 components	2/27 (7%)	2/47 (4%)	2/86 (2%)	4/69 (6%)

Table 16. Criteria of EAD by Preservation Method

The PROTECT trial used a dichotomous definition for EAD events based in three main components (AST, Bilirubin, and INR). The relative contribution of each criterion to the severity of EAD events is not characterized using this definition. Therefore, it is challenging to evaluate the severity of EAD events, given these limitations in this definition of EAD

The panel will be asked the significance of early allograft dysfunction (EAD), when EAD is driven primarily by transaminase (AST), while bilirubin and international normalized ratio (INR) are lower and are not very different between the OCS arm and the Control arm.

An exploratory subgroup analysis of results for incidence of EAD is provided in Table 17 below.

Table 17. Exploratory Subgroup Analysis for Incidence of EAD
(N=296 in mITT Population)

	OCS (N=151)	Control (N=145)	OSC - Control Difference
	n/N (%)	n/N (%)	Δ EAD rate (%)
Fatty Liver Recipients			
Macrosteatosis ≤ 20%	24/147 (16.3)	38/134 (28.4)	-12.0
Macrosteatosis >20%	2/4 (50.0)	4/4 (100.0)	-50.0
Donor Age			
≤ 50	17/82 (20.7)	31/82 (37.8)	-17.1
>50	9/69 (13.0)	15/63 (23.8)	-10.8
MELD Score			
≤ 25	8/45 (17.8)	14/39 (35.9)	-18.1
>25	18/106 (17.0)	32/106 (30.2)	-13.2
DBD Cross Clamp Time			
< 6 hours	2/34 (5.9)	18/82 (22.0)	-16.1
≥6 hours	17/89 (19.1)	17/50 (34.0)	-14.9
Donor Inclusion Criteria (each criterion separately)			
Age ≥ 40	16/102 (15.7)	20/91 (22.0)	-6.3
Expected Cross Clamp Time ≥ 6 hours	11/47 (23.4)	20/56 (35.7)	-12.3
DCD and Age≤ 55 years	7/28 (25.0)	11/13 (84.6)	-59.6
Steatotic Liver	18/93 (19.4)	26/87 (29.9)	-10.5
Donor Inclusion Criteria (single vs. multiple)			
Meets Single Donor Inclusion Criteria	7/57 (12.3)	20/60 (33.3)	-21.1
Meets Multiple Donor Inclusion Criteria	19/94 (20.2)	26/85 (30.6)	-10.4
DCD or DBD			
DCD	7/28 (25.0)	11/13 (84.6)	-59.6
DBD	19/123 (15.4)	35/132 (26.5)	-11.1

In every subgroup in this analysis, EAD was higher in the Control group than in the OCS group. These subgroup analyses for the incidence of EAD, were performed in subpopulations with standard and acceptable donor/recipient cut off values. The number of cases included in these analyses was limited and did not account for other EAD risk factors. The results from these analyses should be interpreted with caution.

Table 18 provides EAD incidence rates per site and arm for completers (N=296). Taking into consideration six centers with 79% of the total enrollment, EAD ranged from 0% to 18% in the OCS arm and from 8% to 50% in the Control group. Among the sites, there was high variability of EAD incidence rates with p-values for pooled site by treatment interaction as 0.1852 and 0.1992 in PP and

mITT populations, respectively.

Table 18. Frequency Table for EAD incidence Rate by Site and Treatment Group (mITT population, n=296)

SITE	OCS		Control		Total (#randomized pts)
	# PTS	EAD (%)	#PTS	EAD (%)	
LV-01-(b) (6)	33	6 (18.2)	36	17 (47.2)	69
LV-02-(b)(6)	23	5 (21.7)	22	3 (13.6)	45
LV-03-(b)(6)	4	0 (0)	1	1 (100)	5
LV-04-(b)(6)	25	4 (16)	18	3 (16.7)	43
LV-05-(b)(6)	2	2 (100)	3	1 (33.3)	5
LV-06-(b)(6)	22	0 (0)	25	2 (8)	47
LV-07-(b)(6)	2	0 (0)	3	1 (33.3)	5
LV-08(b)(6)	3	1 (33.3)	3	0 (0)	6
LV-09-(b)(6)	11	2 (18.2)	8	4 (50)	19
LV-10-(b)(6)	5	1 (20)	7	3 (42.9)	12
LV-11-(b)(6)	3	0 (0)	4	1 (25)	7
LV-12-(b)(6)	1	1 (100)	3	1 (33.3)	4
LV-13-(b)(6)	5	0 (0)	2	2 (100)	7
LV-14-(b)(6)	5	2 (40)	4	3 (75)	9
LV-15-(b)(6)	3	1 (33.3)	1	1 (100)	4
LV-17-(b)(6)	1	1 (100)	0	0 (0)	1
LV-19-(b)(6)	0	0 (0)	1	1 (100)	1
LV-20-(b)(6)	3	1 (33.3)	4	3 (75)	7
	151		145		296

6.5.4 Secondary Effectiveness Endpoint Results

OCS Donor Liver Assessment

The PROTECT trial met the prespecified secondary endpoint performance goal of at least 85% of donor livers preserved using OCS for the entire preservation period. The OCS Liver System device monitors several aspects of donor organs during preservation, as shown in Table 19, below. Assessments were successfully made for 144 out of 155 organs perfused on the OCS.

Table 19. First Secondary Endpoint – OCS Liver Assessment Parameters During Perfusion

OCS Liver System Assessments During Perfusion	**N= 155***
Lactate Level	94%
Hepatic Artery Pressure	100%
Portal Vein Pressure	100%
Average Bile Production Rate	99%
* p-value =0.002 from a one-sided exact binomial test, testing the null hypothesis that the true proportion is less than or equal to 0.85 vs. the alternative hypothesis that it is greater than 0.85.	

The following table summarizes the line data of machine perfusion parameters provided by the sponsor:

Table 20. OCS Liver Machine Perfusion Parameters During Perfusion

Perfusion Parameter	**Min**	**Max**	**Mean**
PF L/min	1.19	2.39	1.95
HAP mmHg	32.63	103.95	70.76
HAF L/min	0.16	0.91	0.65
PVP mmHg	1.00	13.91	5.39
PVF L/min	0.81	1.65	1.29
Resistance in HA* (mmHg x min/L)	45.24	505.28	121.59
Resistance in PV* (mmHg x min/L)	0.73	14.78	4.26

*Calculated parameter

14% of livers preserved on the OCS were reported to have a mean portal vein pressure greater than 8 mmHg, which is considered physiological hypertension. 7.7% of livers preserved on OCS were reported to have a portal vein resistance greater than 7 mmHg x min/L, which is considered physiologically elevated. No correlation was found between post-transplant EAD within the first seven days and livers

perfused at higher than physiological pressures or resistance.

6.5.5 Recipient Survival and Graft Survival

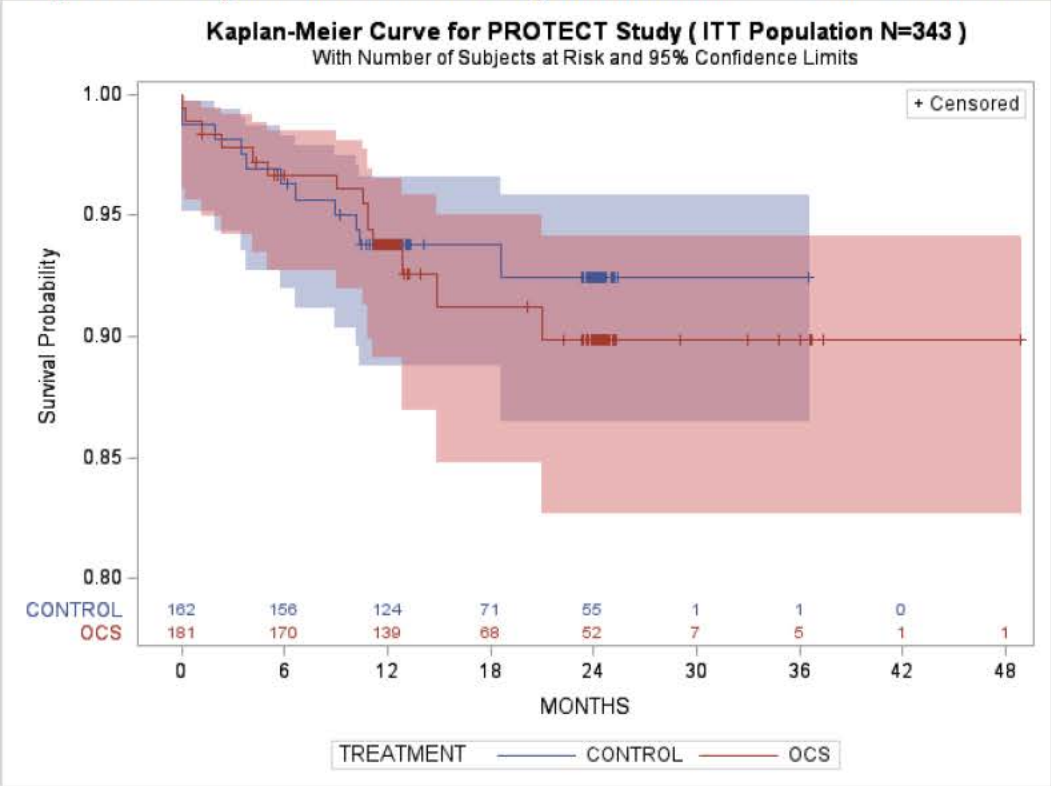
Since the protocol did not specify a method for multiplicity adjustment to control the study overall type I error, p-values and statistical inference are not presented for these secondary effectiveness endpoints. All recipients are analyzed as randomized in this section's results. From Table 21, one can see the observed survival rates are very similar between two arms at day 30 and at time of initial hospital discharge post liver transplantation in the mITT population.

Table 21. Secondary Effectiveness Endpoints: Survival at Day 30 Post-transplantation and at Initial Hospital Discharge Post Liver Transplantation

Population	OCS Treatment % (n/N)	Control % (n/N)	% Difference (OCS- Control)
Survival at Day 30			
mITT (N=298)	99.3 (151/152)	99.3 (145/146)	0.0
PP	99.3 (150/151)	99.3 (141/142)	0.0
Survival at Time of Initial Hospital Discharge Post Liver Transplantation			
mITT	98.7 (150/152)	98.6 (144/146)	0.1
PP	98.7 (149/151)	98.6 (140/142)	0.1

Recipient survival for longer follow-up time is presented in Figure 17 and Table 22 for the ITT group, which includes 343 of 428 randomized recipients. (ITT includes 43 recipients who were transplanted off study with cold storage livers.) Figure 17 show the Kaplan-Meier curves, which are the visual representations of survival function that shows the probability of survival at a respective time interval. The blue line represents Control, the red line represents the OCS, and the shaded areas represent 95% confidence limit at each time point. The data show no difference in recipient survival between the OCS arm and Control arm, since there is no clear separation in Kaplan-Meier curves between OCS and Control arms, and the shaded area are sufficiently overlapped. The 6-month survival was comparable across the OCS (96.7%) and Control (96.3%) arms. The 12-month survival rates are 93.8% for OCS and 93.8% for Control; 24-month survival rates are 90.0% for the OCS and 92.5% for the Control. The lower EAD rate observed in the OCS arm were not reflected in better survival compared to the Control group.

Figure 17. Recipient Survival in ITT Population for the OCS and Control arms



Generated by the FDA reviewer
Source: the sponsor's submitted datasets in the amendment

Table 22. Death at Month 6, 12 and 24 (ITT Population, N=343)

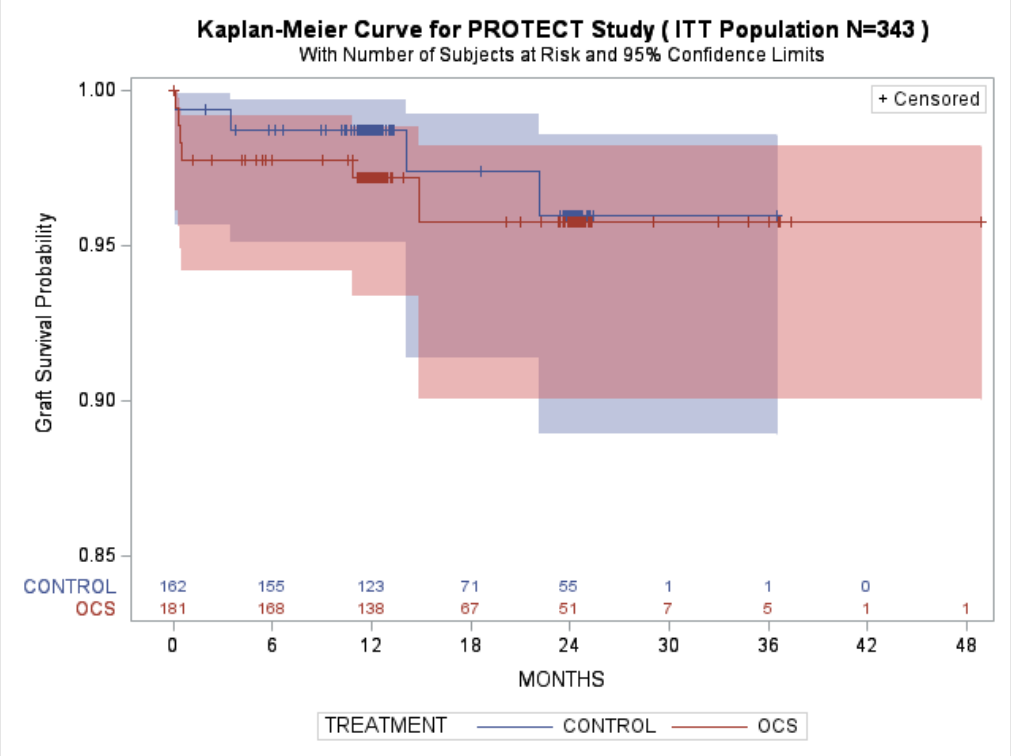
	OCS (n=181)				Control (n=162)			
	# death	%survival*	# at risk	# censored	# death	%survival*	# at risk	# censored
Month 6	6	96.7	170	5	6	96.3	156	0
Month 12	11	93.8	139	31	10	93.8	124	28
Month 24	14	90.0	52	115	11	92.5	55	96

*: Kaplan-Meier estimated rates

Generated by the FDA reviewer
Source: the sponsor's submitted datasets in the amendment

The sponsor also collected graft survival data at 6, 12, and 24 months post-transplant. Graft survival is defined as time from transplant to graft failure, censoring for death with a functioning graft and grafts still functioning at time of analysis based on the sponsor's submitted SAS programs. Figure 18 presents the Kaplan-Meier curves showing the probability of freedom from graft failure, i.e., graft survival probability, at a respective time interval. The blue line represents Control, the red line represents the OCS, and the shaded areas represent 95% confidence limit at each time point. The data show no difference in graft survival between the OCS arm and Control arm. Rates of graft loss at 6, 12, and 24 months are 97.8%, 97.2%, 95.8% and 98.8%, 98.8%, 96.0% for OCS and Control, respectively as shown in Table 22.

Figure 18. Graft Survival (Death Censored) in ITT Population for the OCS and Control arms



Generated by the FDA reviewer
Source: the sponsor's submitted datasets in the amendment

Table 23. Graft Loss (Death-Censored) at Month 6, 12 and 24 (ITT Population, N=343)

	OCS (n=181)				Control (n=162)			
	# graft loss	% graft survival *	# at risk	# censored	# graft loss	% graft survival*	# at risk	# censored
Month 6	4	97.8	168	9	2	98.8	155	5
Month 12	5	97.2	138	38	2	98.8	123	37
Month 24	6	95.8	51	124	4	96.0	55	103

*: Kaplan-Meier estimated rates

Generated by the FDA reviewer
Source: the sponsor's submitted datasets in the amendment

As discussed in section 6.5.1, 11% of 343 recipients had at least 2 randomizations and although the PROTECT trial was designed as a randomized trial, the randomization was impacted by the repeat randomization, and we have observed the OCS arm had significantly more DCD with age ≤ 55 years donors compared to control arm which is presented in section 6.5.2. Therefore, the Agency performed additional exploratory survival analyses based on propensity score analysis which confirmed that the OCS and control groups have similar graft and recipient survival K-M curves. More details on this analysis is included in Appendix 2.

The panel will be asked to discuss the significance of the survival results.

6.5.6 Safety Endpoint Results

The safety assessment was based on the number of liver-graft related serious adverse events (LGRSAEs) through 30 days post-liver transplantation per recipient, consisting of primary non-function, ischemic biliary complications, vascular complications or liver allograft infections. Results presented in Table 24below demonstrate that the average number of LGRSAEs per recipient within the first 30 days post-transplantation in the OCS arm was numerically lower than the Control arm.

Table 24. Liver Graft Related SAEs within 30 Days (AT Population, n=299)

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

Table 25 below shows that at 6 months post-transplant, there was a trend in reduction of the ischemic biliary complications and vascular complications in the OCS arm versus the Control arm.

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Table 25. LGRSAEs within 6 months (AT Population, n=299)

Variable	OCS (N=153)		Control (N=146)	
	Number of Recipients (%)	Number of Events	Number of Recipients	Number of Events
Recipients with at least one LGRSAE within 6 months post-transplant	9 (5.9%)	10	23 (15.8%)	28
Non-functioning graft	0	0	0	0
Ischemic biliary complications	2 (1.3%)	2 (20%)	12 (8.2%)	12 (42.9%)
Vascular complications	7 (4.6%)	8 (80%)	12 (8.2%)	15 (53.6%)
Liver allograft infections	0	0	1 (0.7%)	1 (3.6%)

The OCS and Control arms reported similar mean intensive care unit (ICU) stays (107 and 111 hours, respectively) as well as mean hospital stays (12 and 11 days respectively) in the AT population.

The panel will be asked to discuss the significance of the rates of LGRSAEs.

6.5.7 Pathology Results

Liver biopsies were taken at three timepoints during the liver retrieval and transplantation:

- at the time of donor liver pre-retrieval,
- post-OCS and Control preservation prior to transplantation and
- 90-120 minutes post-reperfusion of the transplanted liver.

A composite sample score that averages three sample timepoints was provided by the core lab to the Sponsor. Samples were analyzed for portal inflammation, lobular necrosis, lobular inflammation, lobular steatosis, liver sinusoidal endothelial cell evaluation, liver fibrosis, and extra-hepatic bile duct score. Additional information about how samples were scored is provided in Appendix 3. The final composite score, range is from 0 to 3 (0 representing No Composite Damage, 3 Representing Severe Composite Damage). No overall differences were seen between the OCS and control tissue sample scores as outlined in Table 26 below.

Table 26. Results of the Average Pathology Sample Scores for the Three Samples Timepoints (AT population, n=299 and PP population, n=293)

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

The results of the Average Pathology Sample Scores presented in Table 26 above by the sponsor as an average of means for the three sample timepoints of the PROTECT trial report shows that there were no significant differences between the OCS arm and the Control arm regarding the pathology scores. However, the Agency believes the results should have provided the comparison of the mean scores separately for each one of the three biopsies (pre retrieval, post preservation and post reperfusion. The sponsor has provided the average of all scores for these three time points. The assessment of the score changes during the preservation time to see whether the changes in one arm are significantly different than the other arm would have provided useful insight.

The sponsor states that the reduction of EAD in the OCS group was "validated mechanistically by the histopathological assessment of liver grafts post-transplant." Figure 19 below includes a post-transplant assessment of the incidence of lobular inflammation. Figure 20 below includes a representative lobular inflammation image for a liver randomized to both the OCS and Control groups. The submission states that independent and blind histological assessment revealed significantly less lobular inflammation for the OCS Livers.

Figure 19. Post Transplant Pathology Assessment- Incidence of Liver Lobular Inflammation (mITT population, n=298 population)

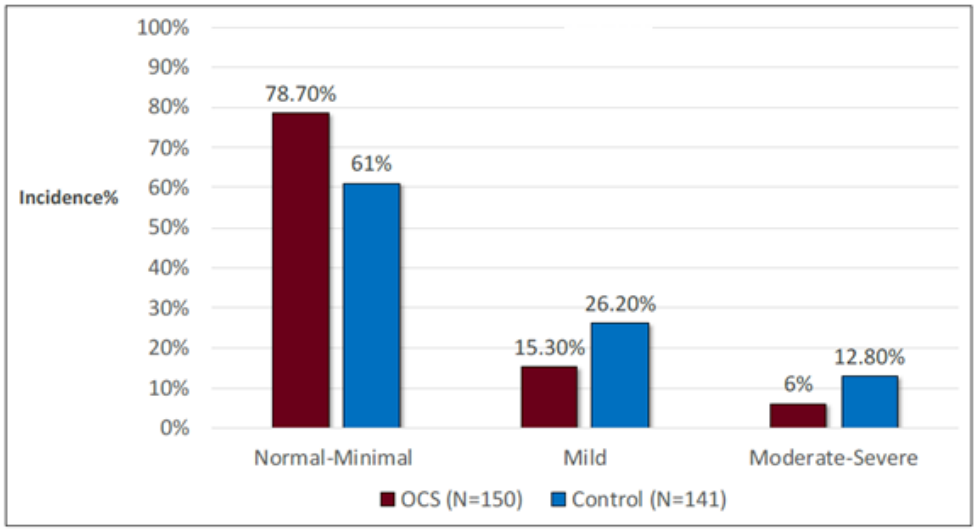
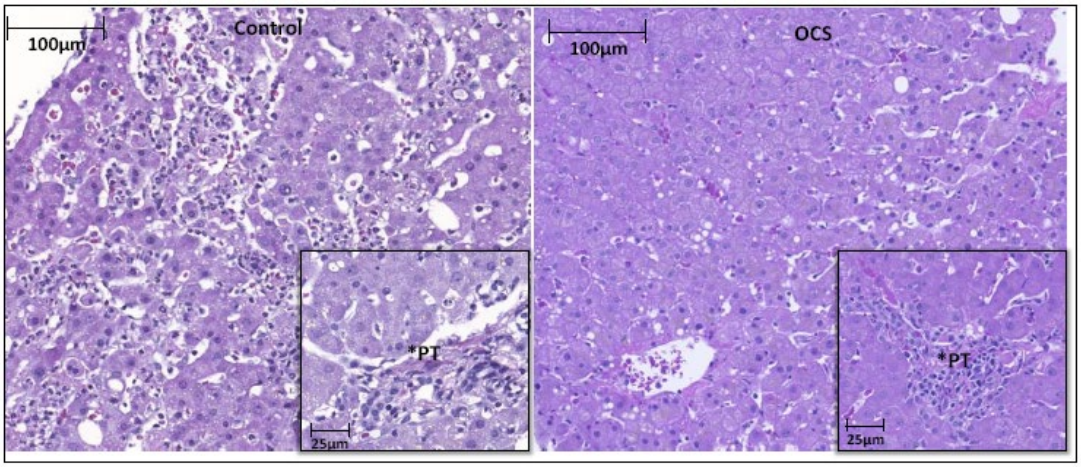


Figure 20. Post-Transplant Histology Representative Sample for Severe Lobular Inflammation



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.

Lobular inflammation is a marker of ischemia and reperfusion injury. It remains unclear why lobular inflammation was reported while other components of the histopathologic assessments were excluded. In addition, although included in the histopathology assessment form, lobular inflammation is not an endpoint described in the protocol.

During interactive review, the Agency asked the sponsor to provide a comparison of the lobular necrosis scores for all three different biopsy times *(pre retrieval, post preservation and post reperfusion) across study arms.* These results are shown below in Table 27.

Table 27. Lobular Necrosis Severity Scores (AT Population, n=299*), Percent Cases with Lobular Necrosis

Histopathology	Pre-Retrieval		Post-Preservation		Post-Reperfusion in the Recipient		Change from Post-Preservation to Post-Reperfusion in the recipient	
	OCS N=153	Control N=139	OCS N=152	Control N=139	OCS N=153	Control N=140	OCS	Control
None/Minimal	95%	96%	78%	94%	56%	52%	-22%	-42%
Mild	2%	4%	16%	5%	26%	28%	+10%	+ 23%
Moderate/Severe	3%	1%	5%	1%	17%	20%	+12%	+19%
Mild/Moderate/ Severe	5%	5%	21%	6%	43%	48%	+22%	+ 42%

*Of the 299 livers included in the AT population, several were missing lobular necrosis scores at various timepoints.

Pre-retrieval biopsies showed similar low percentages, and comparable degree of lobular necrosis across OCS and Control arms.

Post-preservation biopsies showed significantly increased lobular necrosis cases in the OCS arm from 5% (Pre-retrieval) to 21% of the cases (after OCS preservation). In the Control arm, there was no relevant increase in lobular necrosis from 5% (Pre-retrieval) to 6% (after SCS preservation).
Mild lobular necrosis was the severity most frequently observed after preservation. Approximately 14% of the OCS-Livers and 1% in the Control-Livers, sustained a mild lobular necrosis damage during liver preservation.

Post-reperfusion biopsies after transplant showed similar percentages, and comparable degree of lobular necrosis across OCS and Control arms.

Compared to post-preservation biopsies, there was a significant increase in lobular necrosis cases in both, OCS and Control during liver reperfusion in the recipient. Change in the incidence of lobular necrosis from Post-Preservation to Post-Reperfusion increased in twice the numbers of cases in the Control group (+42%) compared to the OCS (+22%) group.

Even though, reperfusion in the recipient will bring an amplified reperfusion injury in both OCS and Control, it is not well defined why the reperfusion injury appears to be in higher numbers in the Control compared to OCS.

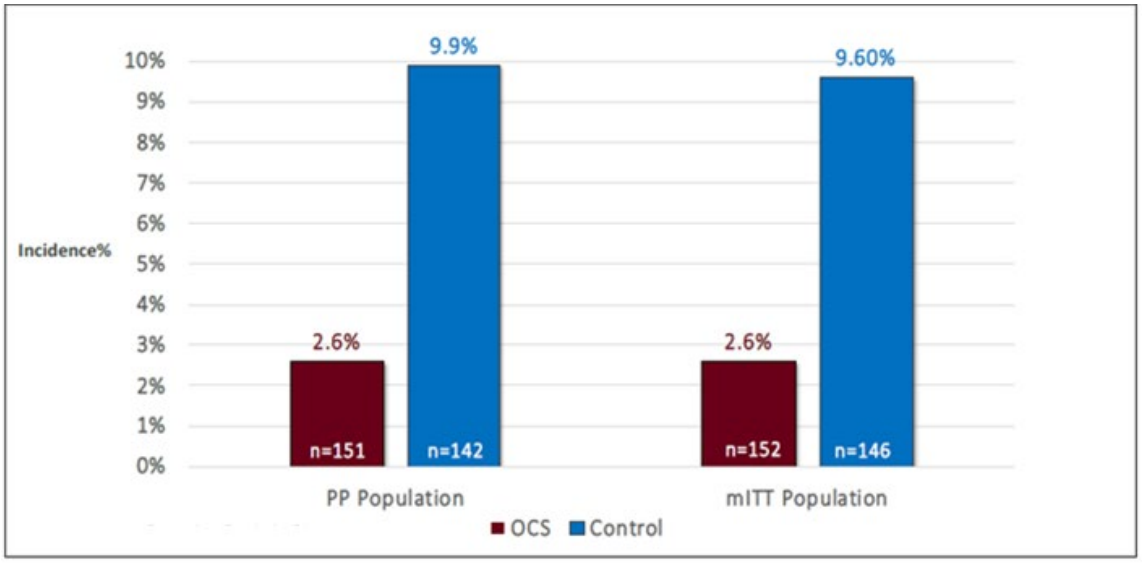
The Agency believes that post-reperfusion numbers can be compared to the post-preservation numbers which can provide information about the "warm ischemia time" during the surgery when the liver is being implanted not necessarily about the preservation injury. Surgeons generally try to keep this implantation (anastomosis) time as short as possible, because the organ sustains a certain level of warm ischemia injury until all the anastomoses are complete and the vascular clamps are removed to let the blood circulation begin (reperfusion).

On the contrary the sponsor states that any changes seen in Timepoint 2 should not be compared across groups given that the oxygenated blood perfusion condition is not applied to both study arms as the two arms in the protect trial are recipiented to different biological environments. The sponsor states that the most clinically relevant timepoint is when both OCS and Control liver allografts are perfused in the recipient's abdomen post-transplantation (i.e., Timepoint 3, post-reperfusion in the recipient's abdomen). At this timepoint, both study arms are recipiented to the same physiologic environment and, as can be shown in Table 1 below, lobular necrosis is similar, with the Control group showing slightly more moderate/severe necrosis than the OCS group.

6.5.8 Ischemic Biliary Complications

The Agency recommended the sponsor include a safety endpoint of the incidence of ischemic and non-ischemic biliary complications at 6 and 12 months. The incidence of non-ischemic biliary complications was not included in the Statistical Analysis Plan (SAP) as an endpoint, and there was no prespecified methodology to detect subtle subclinical cases. However, the Sponsor collected non-ischemic biliary complications as part of the LGSAE safety endpoint following the standard of care of individual centers for the detection of these complications. The sponsor reports the incidence of ischemic biliary complications in the PROTECT trial in the figure below.

Figure 21 Incidence of Ischemic Biliary Complications from Day of Transplantation through 12 Months



During review of the PMA, the Agency has expressed concern about verifying the claim of superiority in ischemic biliary complications, because of the absence of a protocol-specified definition of ischemic biliary complications and diagnostic criteria. FDA asked the sponsor to describe how and what type of diagnostic information (such as magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), hepatobiliary iminodiacetic acid (HIDA) scan or percutaneous transhepatic cholangiogram (PTC) and biopsy, etc.) was collected and scored to make the diagnosis of ischemic biliary complications. The sponsor replied that the collection of ischemic biliary complications was prespecified and defined as "ischemic biliary strictures and non-anastomotic bile leaks". They state the method of diagnosis was

intentionally not prescribed in the protocol to focus on clinically relevant events and to avoid interfering with the trial center's internal standard clinical practice for liver transplant recipients' post-transplant management." Every recipient who was diagnosed by trial site was confirmed by ERCP or MRCP. The CEC, who were blinded to the study groups, independently adjudicated the diagnosis via review of the ERCP or MRCP reports. The Agency believes that every study endpoint and the methods for data capturing and diagnostic criteria should be clearly defined in the study protocol. This was not the case for the ischemic biliary complications endpoint which raises questions about the ischemic biliary complications endpoint.

The panel will be asked to discuss whether the study results support a claim of reduction of ischemic biliary complications.

Ad Hoc Analysis of Biliary Complications

Table 28 below shows an ad hoc analysis was performed to assess biliary complications captured as Serious Adverse Events, which were diagnosed by various clinical institutes. There was no established protocol to detect undefined biliary complications (ischemic and non-ischemic) and therefore, it is challenging to draw conclusions about the incidence of these complications across arms.

Table 28. Ad Hoc Analysis of Ischemic and Non-ischemic Biliary Complications (AT population, n=299)

	OCS (N=153)	**Control (N=146)**
Incidence of Ischemic Biliary Complications from Day of Transplant through 6 Months Follow-up Visit.	1.3%	8.2%
Incidence of Ischemic Biliary Complications from Day of Transplant through 12 Months Follow-up	2.6%	9.6%
Biliary complications Diagnosed at 30 Days Post-Transplant	13/153	8/146
Non-ischemic biliary complications Diagnosed at 30 Days Post-Transplant	13/153	6/146
Ischemic biliary complications Diagnosed at 6 Months Post-Transplant DCDs	1/28	2/13
Ischemic biliary complications Diagnosed at 6 Months Post-Transplant	2/153	12/146
Ischemic biliary complications Diagnosed at 12 Months Post-Transplant DCDs	1/28	2/13
Ischemic biliary complications Diagnosed at 12 Months Post-Transplant	4/153	14/146

6.5.9 Post reperfusion syndrome (PRS)

In Table 29 below, the sponsor also reported the extent of reperfusion syndrome as assessed based on

decrease of lactate levels.

Table 29. Assessment of Reperfusion Syndrome – Recipients' Lactate Levels ~120 Minutes Post-Reperfusion in Recipient (mITT Population, n=299)

	OCS	Control
Recipients' Lactate Level	3.64 ± 2.220	4.33 ± 2.987

Reperfusion Syndrome was more severe in the Control group compared to the OCS group, as indicated by higher lactate levels. The Agency agrees with the Sponsor regarding the probable clinical benefits of decreasing the incidence of post reperfusion syndrome (PRS); however, PRS definitions, severity, and the numerosity of possible confounding factors, complicates the interpretation.[33]

6.5.10 DCD Liver Results

The PROTECT trial includes two distinct populations: DBD (N=295) and DCD (N=46) liver recipients. The sponsor has proposed an indications for use that specifies both liver allografts from donors after brain death (DBD) and liver allografts from donors after circulatory death (DCD) ≤55 years old. Table 13 provides the demographic and baseline characteristics of the DCD donors. The baseline characteristics indicate the DCD livers included in the PROTECT trial were of reasonable quality and adequate for transplantation.[20,21]

EAD results for DCD livers

As shown in Table 17, EAD rates are lower in the OCS arm for both the DBD and DCD subgroups, but the difference is bigger in the recipients of DCD livers (OCS 7/28 (25.0%), Control 11/13 (84.6%)) than in the recipients of DBD livers (OCS 12/123 (15.4%), Control 35/132 (26.5%).

Survival Results for DCD Livers

Table 30 provides survival results for recipients of DCD livers and DBD livers for the ITT group (e.g., 46 ITT DCD livers; from 41 mITT DCD livers and 5 DCD livers that were transplanted off study with cold storage and are tracked as Control livers). Please note that for Table 30 and the Kaplan-Meier survival curves for DCD and DBD in Appendix 2, recipients are analyzed according to the actual donor liver preservation received as indicated in the table and figures. Recipient deaths are higher in the OCS preserved liver recipients than in the Control (cold storage) preserved liver recipients. For the DCD recipients in the ITT group, 5 of 28 OCS recipients died before 24 months while 1 of 18 recipients in the Control group died. Kaplan Meier survival curves for DCD and DBD livers are provided in Appendix 2. (For the DCD recipients in the mITT group, there were 5 deaths in 28 OCS recipients and 0 deaths in 13 Control recipients.)

Table 30. Recipient Death and Graft Loss (Death-Censored) at Month 6, 12 and 24

Recipient Death at Month 6, 12 and 24								
ITT DCD Population, n=46								
	Preserved by OCS (n=28)				**Preserved by Control (n=18)**			
	#death	**%survival***	**# at risk**	**#censored**	**#death**	**%survival***	**# at risk**	**# censored**
Month 6	1	96.4	27	0	1	94.4	16	1
Month 12	4	85.7	18	6	1	94.4	12	5
Month 24	5	57.1	2	21	1	94.4	7	10
ITT DBD Population, n=295								
	Preserved by OCS (n=124)				**Preserved by Control (n=171)**			
	#death	**%survival***	**# at risk**	**#censored**	**#death**	**%survival***	**# at risk**	**# censored**
Month 6	3	97.6	121	0	6	96.5	161	4
Month 12	5	95.6	102	17	10	94.1	130	31
Month 24	6	94.1	39	79	12	91.8	59	100
Graft Loss (Death-Censored) at Month 6, 12 and 24								
ITT DCD Population, n=46								
	Preserved by OCS (n=28)				**Preserved by Control (n=18)**			
	#graft loss	**%graft survival***	**# at risk**	**# censored**	**#graft loss**	**%graft survival***	**# at risk**	**# censored**
Month 6	0	100.0	27	1	0	100.0	16	2
Month 12	0	100.0	18	10	0	100.0	12	6
Month 24	1	66.7	2	25	1	87.5	7	10
ITT DBD Population, n=295								
	Preserved by OCS (n=124)				**Preserved by Control (n=171)**			
	#graft loss	**%graft survival***	**# at risk**	**# censored**	**#graft loss**	**%graft survival***	**# at risk**	**# censored**
Month 6	2	98.4	119	3	4	97.6	160	7
Month 12	3	97.5	101	20	4	97.6	129	38
Month 24	3	97.5	38	83	5	96.4	59	107

*: Kaplan-Meier estimated rates

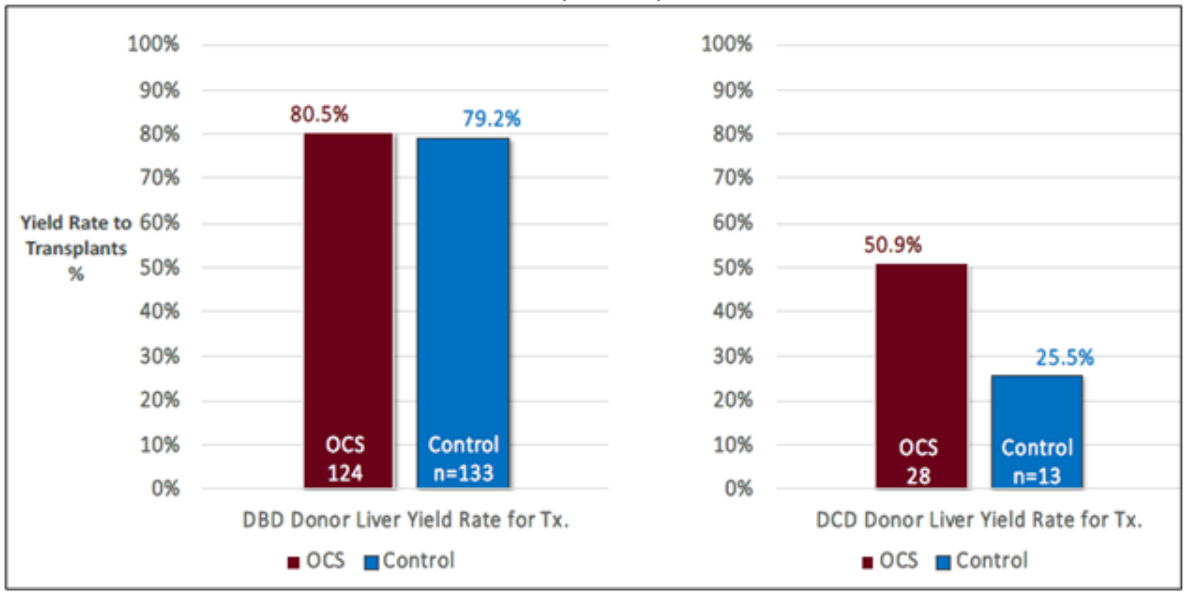
Utilization Rates for DCD Livers

Figure 22 shows the rate of utilization of DCD livers in the mITT group. 106 DCD livers were matched for transplantation. 50.9% (28/55) of the DCD livers randomized to OCS were transplanted, compared to 25.4% (13/51) of the DCD livers randomized to the Control group. (Note that the 13 DCD livers in the Control group is based on the mITT group, and it differs from the 18 DCD livers in Table 30, because Table 30 includes 5 livers that were screen failures, but were transplanted off-study following cold storage.) The sponsor states that the higher rate of recovery of DCD livers for transplantation in the

OCS arm demonstrates the benefit of the OCS assessment capabilities.

As discussed above, the data in Table 13, DCD Donor Demographic and Baseline Characteristics (AT population), show that the DCD livers included in the PROTECT trial were of reasonable quality and adequate for transplantation. Note also that the PROTECT trial was an open-label trial where investigators had knowledge of the trial treatment assignment.

Figure 22. Overall Donor Liver Yield from DBD and DCD donor for Transplantation, PROTECT trial (N=428)*



*Note that there are 476 unique matched donor livers and in the Figure 22, the utilization rates for DCD and DBD are only based on 428 donor livers.

The panel will be asked to discuss whether the data from the study support an indications for use for DCD livers.

6.6 Device Malfunctions

In the PROTECT trial, the sponsor reports three device malfunctions in the OCS arm, one of which resulted in the organ transfer to cold static storage for transplantation and subsequently a major protocol violation. Device malfunctions were defined by the sponsor as failure of a clinical device to meet its performance specifications or otherwise perform as intended thereby presenting a potential for injury to a recipient or user. Table 31 provides a summary of the device malfunctions and the associated recipient and graft outcomes.

Table 31. Summary of Device Malfunctions and Associated Recipient and Graft Outcome

Recipient	Transplant Date	Malfunction Description	Was the Organ Transplanted?	EAD Y/N?	Graft Survival	Recipient Survival
Malfunction 1	9/8/2019	SDS Cassette infusion line would not stay connected to the Console. A broken retaining plastic tab was identified on the SDS Cassette. A spare SDS Cassette was used and the OCS session proceeded without further incident.	Yes, on OCS	No	Survived as of day 394	Alive as of day 394
Malfunction 2 B	3/11/2019	Perfusion module was not recognized by the OCS device.	Yes, on ice	No	Survived as of day 345	Alive as of day 345
Malfunction 3	11/5/2018	PV valve used to flush organ at the end of the OCS perfusion session malfunctioned which resulted in the team flushing directly through the PV cannula. The flush proceeded without incident and the liver was transplanted.	Yes, on OCS	Yes (DCD donor)	Survived as of day 382	Alive as of day 382

These device malfunctions resulted in one protocol violation but did not cause any harm to the recipients involved. The reasons for these malfunctions included an electrical connection issue, a break in the plastic housing for an IV infusion line, as well as a portal vein value malfunction. In two of these cases, the mechanical failure occurred before the organ was placed on the device. In the case where the organ was placed on the device, the users were able to mitigate the malfunction through a manual procedure.

While the cases reported in the PROTECT trial were minor, the Agency is concerned about the potential for device malfunctions to result in liver damage or breach of organ sterility. Although the malfunctions discussed here did not result in recipient harm, the OCS is complex and requires a more demanding transplant workflow to manage than the cold storage standard of care. The risks of device malfunction are in part mitigated by organ transfer to cold static storage, as was done in the case of the electrical connection error in the table above, but the possibility of organ damage due to device malfunction on the OCS is greater than that of cold static storage. The potential for additional device related adverse events is typically balanced by improved clinical outcome as discussed further in section 7 (FDA's Benefit Risk Decision Making).

The panel will be asked to discuss the significance of the device malfunctions.

6.7 Turndown Organs

6.7.1 Turndown Organ Recipient Narratives

Three DCD livers were turned down after perfusion on the OCS device. These three donor livers were deemed "non transplantable" following OCS preservation although initially they were assessed as "transplantable" following donor organ retrieval surgery prior to placement on the OCS device. The sponsor states the three turned-down livers were rejected because of biopsy results or increasing lactate levels in their perfusion fluid. The sponsor indicates these cases were not "device malfunctions, or mechanical errors." The sponsor also notes that these DCD liver turndowns should not be considered a negative event, because during the clinical trial many DCD livers were utilized for transplant. They further indicate their device provides additional prospective assessment capabilities of donor liver function and metabolic condition that can be used to help to increase the donor pool of DCD livers. The sponsor states that DCD livers are riskier and less utilized, so it is not unexpected to have a small number of DCD livers turned down for transplant.

As stated earlier, DCD livers like those included in the PROTECT trial (livers of age < 50 years with < 6 hours of cold ischemic time) have been shown to have superior graft survival when compared to older DBD livers (≥ age 60 years).[21] Therefore, the Agency has questions related to whether or not these livers were damaged by the OCS system, (as suggested previously in section 6.5.7 Pathology Results - Table 27), and would otherwise have been transplanted successfully, if they had been preserved with cold storage. The following tables 32-34, summarize what was shared with the Agency about the turndown livers in the Turndown Narratives provided in the PMA.

Table 32. Summary of Turndown Livers Recipient Narratives

Recipient	Transplant Date	Donor Description	Donor Organ Description (prior to OCS preservation)	Time on OCS	Baseline lactate/Final Lactate, enzymes	Reason for turndown
Turndown 1		19-year-old male DCD donor that died due to rejection of lung transplant.	The pre-preservation biopsy already showed changes of hepatocyte injury manifest primarily as hepatocyte swelling, Mallory-Denk-like biopsies, and cytoaggregation and separation from adjacent cells. The already present changes became	166 minutes	Baseline: 10.08 mmol/L Final: 10.98 mmol/L Baseline AST: 4017 U/L ALT: 3063 U/L	Turned down for high lactate levels and low pH in perfusate

			substantially worse in the post-preservation biopsy.			
Turndown 2		46-year-old female who died from anoxia.	Initial biopsy showed platelet-fibrin thrombi Final biopsy: widespread cytoagregation and early necrosis more prominent in left lobe than right. There is widespread early coagulative-type necrosis predominantly involving perivenular with lesser periportal and random locations. Some perivenular congestion is also present with hemorrhage into the space of Disse in the perivenular regions. The portal vein branches do not appear to be well-perfused and occasional platelet-fibrin thrombi similar to those seen in the baseline biopsy are also seen in this specimen.	158 minutes	Baseline: 9.9 mmol/L Final: 10.25 mmol/L Baseline: AST:3175 U/L ALT:2826 U/L Final: AST:4224 U/L ALT: 3773 U/L	Turned down for high lactate levels

Turndown 3	6/19/2019	29-year-old female DCD donor with significant cardiac history (tetralogy of Fallot repair at age 6, congestive heart failure) and recent admission for possible endocarditis, who arrived to emergency department after suffering cardiac arrest at home on June 10, 2019. Arrest was witnessed and CPR was immediately initiated by donor's father. Time between withdrawal of support and initial donor flush was 34 minutes.	Liver was harvested 30 minutes after donor death to cross-clamp. No visual variances and a biopsy sample was taken from right lobe.	102 minutes	Baseline: 11.11 mmol/L Final: 7.73 mmol/L	Donor biopsy report notes fibrosis expansion in most portal areas and recipient cite turned down the organ due to "bridging fibrosis" from the donor pathology slides.

6.7.2 Turndown Organ Liver Biopsy Results

Of the three lost livers, one was turned down for bridging fibrosis, which was identified in the pre-transplant biopsy and the two other livers were identified by high, rising lactate levels on the OCS device. For the organ turned down for bridging fibrosis, it is unclear how severe and extensive the bridging fibrosis was because the final whole pathology report showed no lobular fibrosis. Rising lactate levels is a sign of inadequate perfusion and inadequate oxygenation as lactate is produced when there is inadequate circulation and oxygenation.[34,35] This could raise questions about a device malfunction due to insufficient perfusion/oxygenation of the livers while on the OCS. Lactate accumulation is the product of anaerobic respiration under warm conditions. There are no cases in the Control arm that resulted in primary non-function (PNF), Note: (PNF) is defined as an aggravated form of reperfusion injury resulting in irreversible graft failure without detectable technical or immunological problems.

Table 33. Donor Biopsy Results – Pre-Retrieval

Recipient ID	Lobular Steatosis:	Fibrosis	Portal Inflammation:	Lobular Inflammation:	Lobular Necrosis:
Turndown 1	0%	none	None	minimal	minimal
Turndown 2	0%	none	None	none	none
Turndown 3	0%	Mild/Moderate	Minimal	mild	mild

Table 34. Whole Liver Evaluation – Post-Turn Down

Donor	Lobular Steatosis:	Fibrosis	Portal Inflammation:	Lobular Inflammation:	Lobular Necrosis:	Diagnosis
Turndown Liver 1	0%	none	none	none	SEVERE	Severe Preservation/ex-vivo reperfusion injury
Turndown Liver 2	5%	none	none	none	SEVERE	Severe Preservation/ex-vivo reperfusion injury
Turndown Liver 3	0%	none	minimal	mild	MODERATE	Severe Preservation/ex-vivo reperfusion injury

Per the pre-retrieval versus post retrieval pathology comparisons, in one of the three livers there was no necrosis pre-retrieval but severe necrosis post preservation (Turndown Liver 2). In the remaining two livers, (Turndown Livers 2 and 3 and) there was mild necrosis pre retrieval which became much worse post preservation. Therefore, there was inadequate perfusion and/or oxygenation during OCS preservation. The pathologist comments that all these post preservation increased necroses are the result of pre retrieval damage, but the biopsy reports show that preexisting minimal damage significantly increased post preservation. The Agency believes the likely explanation for rising lactate levels in the perfusate during the OCS preservation is inadequate perfusion/oxygenation; the sponsor believes that the OCS may have identified undetected issues in the transplanted organs that could not have been observed with cold storage.

The Agency currently believes that there is credible evidence that there is a system malfunction component. This credible evidence is the rising lactate levels in the perfusate. Lactate (or lactic acid) is the end product of anaerobic respiration. High lactate levels are observed in hemorrhagic shock or septic shock recipients in whom there is inadequate blood circulation and hypoxia. High lactate in the perfusate shows that instead of aerobic respiration, anaerobic respiration has started in the preserved organ. The premise of the normothermic perfusion is to maintain aerobic respiration without causing hypoxia in the preserved organ.

6.7.3 Effect of Organ Turndowns on Recipient Surgery

The Agency is concerned that the possibility of turning down an organ after donor/recipient matching may increase the risk of unnecessary surgery in a sick recipient population. It is a common practice to start recipient surgery before the donor liver arrives at the recipient center to minimize cold ischemia times.[36,37] This is especially true for donation after cardiac death (DCD) donor transplantations.[38]

During Interactive Review, the Agency asked the sponsor to clarify the status of the recipient surgery when the donor organ was deemed not acceptable for transplant. The sponsor clarified that in all three cases of turndown organs, skin incisions were not made, and recipients were not harmed or endangered. The results are summarized in table 35 below.

The panel will be asked to discuss the significance of the liver turn downs.

The panel will be asked whether the OCS Liver System adequately assesses donor livers to make decisions regarding subsequent transplantation of the donor livers.

Table 35. Recipients Perioperative Data

Patient	Brought to the OR	ET intubation	Arterial and intravenous lines	Surgery started
Turndown 1	yes	no	no	no
Turndown 2	yes	yes	yes	no
Turndown 3	Pre-op area	no	no	no

The Agency notes these are high risk recipients for general anesthesia so even though a skin incision was not made, the risk to the recipient who underwent anesthesia was significant.

In summary, in the PROTECT trial there were two organs turned down as a result of being assessed by the OCS System (due to high lactate). There were no such reported occurrences (turndown livers) in the Control arm. The Agency is concerned that the OCS System's assessment of the organ during preservation may lead to more organs being turned down after they were already deemed acceptable for transplant, which may in turn lead to an increased risk of unnecessary recipient surgery than would have otherwise occurred using cold static storage. The sponsor states that use of the OCS System removes the time constraints of the transplant team to mobilize the liver, since it is not necessary to minimize ischemic time for the donor graft when using the OCS System. They further state that DCD liver turndown based on OCS assessment (high lactate) should not be considered a negative event because they believe these livers were damaged prior to placing them on the OCS device. It is not clear how these particular DCD organs would have performed if transplanted using the Control.

6.7 Trial Monitoring

After Part A of the trial (the first 20 recipients), at FDA's request, the sponsor implemented a clinical events committee (CEC) comprised of three experienced experts in the field (two liver transplant surgeons and one liver transplant hepatologist) to review trial events. The CEC met periodically to review and adjudicate EAD, adverse events, and deaths to provide consistency in the categorization of such events. In addition, protocol deviations were also adjudicated to either minor or major. Event adjudication was performed in accordance with the pre-specified definitions in the trial protocol and in accordance with the CEC charter.

After Part A of the trial the sponsor also instituted a Data Safety Monitoring Board (DSMB) comprised of a liver transplant surgeon, liver transplant hepatologist, and an independent biostatistician, to monitor the trial. The DSMB met periodically and made recommendations to the Sponsor regarding continuation, modification, or termination of the trial, as outlined in the DSMB charter.

6.8 Major Protocol Violations

The Major Protocol Violations which occurred during the PROTECT trial are summarized in Table 36 below.

Table 36. Summary of Major Protocol Violations

Randomization Assignment	Recipient	Deviation Type	Description
OCS	Malfunction 2	Recipient randomized to OCS, but organ preserved on cold storage	Recipient was randomized to OCS, but organ was preserved on cold storage due to device malfunction prior to organ instrumentation. The recipient was successfully transplanted. A description of the device malfunction is as follows: During setup of the system at the donor site, the system displayed the message "Perfusion Module Not Present" even though the Liver Perfusion Module was installed. Despite attempts to reinstall the module, it was not recognized as being installed in the system.
Control	Violation 2	Recipient randomized to Control but received OCS preserved organ	This recipient received a liver preserved on the OCS that was originally intended for another Recipient, (b) (6) Recipient (b) (6) was found to have metastatic cancer at the time of transplant surgery and the transplant procedure was aborted. The local OPO reallocated the organ to Recipient (b) (6). Although (b) (6) was randomized to Control, the Recipient received the organ being maintained on OCS. The recipient was successfully transplanted.

Control	Violation 3	Donor Eligibility Criteria	The donor organ for this recipient was noted to have accessory vessels post-transplantation upon operative report review.
Control	Violation 4	Donor Eligibility Criteria	The donor organ for this recipient was noted to have accessory vessels post-transplantation upon operative report review.
Control	Violation 5	Donor Eligibility Criteria	The donor organ for this recipient was noted to have accessory vessels post-transplantation upon operative report review.

7.0 FDA's Benefit-Risk Decision Making

7.1 PROTECT Trial Benefits

Of the 476 donor livers uniquely matched to randomized recipients, 176 (37%) were considered as screen failures by the sponsor and 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 raise questions for the Agency and increase uncertainty related to the trial results described below.

The primary effectiveness endpoint in the PROTECT trial was an assessment of EAD. The OCS treatment arm resulted in a 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 significant uncertainty associated with this result. Although, the primary endpoint of this study pertained to incidence of EAD, EAD is intended as a predictor of clinical outcomes, and it may be of less interest than the actual clinical outcomes of recipient and graft survival. The ability of EAD to serve as a reliable predictor of clinical outcomes is explained in the Olthoff[10] publication. In the Olthoff study, the EAD biomarker reliably predicted the increased 6-month mortality and the increased graft loss with an 8-10 fold difference between the EAD recipients versus the non-EAD recipients. However, in the PROTECT Trial, despite a significant difference between the EAD rates at 7 days, no significant difference between the subsequent mortality or the graft loss rates were observed. Given that host and graft survival are the ultimate and 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 we also did not observe 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. 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. Nonetheless, 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.

Three DCD livers were deemed unacceptable for transplant due to rising lactate levels detected by the OCS Liver System. The sponsor also asserts that assessment of the organ on the device resulted in clinical benefits such as identifying poor DCD livers that were unacceptable for transplant due to rising lactate and bridging fibrosis. The detection of unsuitable organs for transplant is a potential benefit of the device. However, as also discussed in the trial risk section below, liver pathology reports showed an increase in organ damage after the turndown organs were perfused for >100 minutes on the OCS-Liver System, so it is unclear if these organs were damaged prior to being placed on the OCS-Liver System or the damaged was caused after being placed on the OCS-Liver System. Finally, the DCD organs used in this study could be considered of higher quality (e.g., from younger donors[22]) and transplantable[21]. Given the high-quality DCD organs used in this trial, it is challenging to assume that these livers would not have done equally well had they been transplanted with cold static storage.

The sponsor reports a benefit in the increased utilization of DCD livers in the PROTECT trial as a higher number of DCD donor livers for transplantation was noted in the OCS arm compared to the Control arm (OCS 50.9% (28/55), Control (13/51) 25.5%). However, there is significant 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 didn't include stratification to ensure equal numbers 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, these results should be interpreted with caution.

The sponsor also claims that the device resulted in a reduction of ischemic biliary complications, reperfusion syndrome, and less 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 sponsor states 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 PROTECT trial met the prespecified secondary endpoint 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 viability 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 September 28, 2020 Major Deficiency Letter, the sponsor states that AST, ALT, bilirubin and lactate levels are common chemistry levels and bile production is the hallmark of liver excretory

function in humans. They state the OCS Liver System provides the organ with an *ex vivo* environment that enables further assessment and monitoring of the organ by clinicians using the same evaluations and assessment methods as they use in the donor's and recipient's in vivo. The sponsor also states they provided FDA with "extensive animal testing results during the IDE review process that validated the relevance of these lab values, and we correlated them with swine liver histology." The Agency believes the animal studies presented during the IDE review were acceptable to support safety for approval of the PROTECT trial. The novel animal study conducted for the PMA was intended only to validate the OCS Liver System design and functionality.

7.2 PROTECT Trial Risks

In the PROTECT Trial there were three DCD livers initially deemed transplantable but later found to be non-transplantable due to high lactate levels(2 organs) and biopsy results (1 organ) after they arrived at the recipient center while the three recipients were in various stages of preparing for surgery. The sponsor also reported three device malfunctions, one of which resulted in transfer to cold storage. In the Control arm, no organs were turned down, no unnecessary recipient procedures (including anesthesia) had been initiated, and no device malfunctions were reported. There is substantial uncertainty around these risks, however. The sponsor states that the unsuitable DCD organs were damaged prior to placing them on the OCS device but the Agency is has questions about this explanation given that turndown liver pathology reports show that the livers preserved with OCS sustained increased lobular necrosis after perfusion with the OCS device. Overall trial pathology report results (AT population=299) show approximately 14% of the OCS-Livers and 1% in the Control-Livers sustained mild lobular necrosis damage during liver preservation. However, reperfusion biopsy results after transplant show comparable degrees of lobular necrosis across OCS and Control arms. Additionally, risks associated with device malfunction can be mitigated through transplant using cold static storage which, while potentially breaking the sterile barrier during organ transport is easy to implement and plan for.

In summary, the OCS device appears to preserve organs similarly to the Control (cold, static storage, CSS), given the lack of difference in clinically relevant outcomes of survival to 12 months, ICU stay, or hospital stay. The benefit of reduced EAD without concomitant improvement in these clinically important outcomes is unclear. There is significant uncertainty around the purported benefits of functional assessment and appropriateness of organs for transplant as described above. Of concern is the fate of livers deemed "not transplantable" after OCS preservation. In addition, while increasing the utilization of DCD organs to expand the overall donor pool would be a notable benefit of any transplant-related device, the inclusion of mostly "high-quality" DCD livers in this trial makes it unclear as to whether these organs would have done equally well with CSS. Further data may be helpful to better understand the role of the OCS device in this regard.

While considering the assessment of benefit and risk, it's important to keep in mind the disproportionate exclusion of livers due to screening failures in the OCS arm due to randomization of recipients prior to assessment of donor livers. This element of the study design introduces uncertainly into the assessment of benefit and risk since it impacted the composition of both study arms and it is challenging to determine its impact on study outcomes.

The complexity of the OCS device compared to CSS provides opportunity for device malfunction. Fortunately, device malfunctions in the trial were able to be mitigated with CSS. It is unknown if this will always be the case in real world use. In addition, a few livers were deemed as not transplantable after preservation with the OCS device. Data from this trial do not allow for determining whether this was due to pre-existing injury or subsequent injury once placed on the OCS device.

8.0 PROTECT Trial Continued Access Trial (CAP) Summary

As of the database closure date of April 8, 2021, all 74 recipients enrolled in the single arm CAP study (all using the OCS device) have reached 30 days post-transplant and 50 recipients have reached 6 months. The trial is ongoing, and data are still being collected, monitored, verified, and adjudicated for all transplanted recipients. A summary of the available data for these 74 recipients is provided in Table 37-39, below. The sponsor reports that donor characteristics are similar, except that PROTECT CAP has a higher percentage of DCD donors (23% in CAP) compared to PROTECT (18%). Recipient demographic and baseline characteristics were similar, except that the PROTECT CAP has a higher percentage of primary hepatic tumors (17.6% in CAP) compared to PROTECT (9.2%). Nineteen (19) recipients experienced EAD within the first 7 days post-transplant, as shown in table 36 below.

Table 37. OCS Liver CAP - EAD Results

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

Table 38. OCS Liver CAP - Recipient Survival/Graft Survival Results

Survival	OCS Subjects (N=74)
30-day Patient Survival	73/74 (98.65%)
30-day Graft Survival	73/74 (98.65%)
6M Patient Survival	45/50 (90.00%)
6M Graft Survival	49/50* (98.00%)
*There was one graft failure (patient (b) (6)).	

As seen in Table 39 there were 5 recipient deaths among the 50 recipients for whom survival data are available. The Agency is concerned that the possible role of the preservation method (OCS) cannot be ruled out in these recipient deaths. As seen in table 38, these deaths occurred on postoperative (POD) 30, 59, 75, 108 and 111, which are all within the 4-month postoperative period. In Table 37, the sponsor indicates that there were no primary nonfunctions (PNF); however, there is one PNF (b) (6) . Per the report, "One recipient, (b) (6) , experienced liver allograft failure starting on POD 0 and was re-transplanted 9 days later." The Agency considers this PNF, but the sponsor provides alternative explanations (hemodynamic instability etc.). Regarding the other deaths, in general, liver allograft dysfunction may potentially result in infections, sepsis and also potentially in ulcerations in the gastrointestinal tract (including duodenal ulcer). The fact that the recipient died of sepsis or peptic ulcer perforation may not be sufficient to rule out liver allograft dysfunction and any possible role of the preservation method for these early deaths.

Table 39. OCS Liver CAP – Recipient Death Summary

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

9.0 Post-Approval Trial Considerations

The inclusion of a Post-Approval Trial (PAS) section in this summary should not be interpreted to mean that FDA has decided on the approvability of this PMA device. The presence of a post-approval trial plan or commitment does not alter the requirements for pre-market approval and a recommendation from the Panel on whether the benefits outweigh the risks. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval trial could be considered. The issues noted below are FDA's comments regarding potential post-approval studies for the Panel to include in the deliberations, should FDA find the device approvable based upon the premarket data.

If the OCS Liver System is approved, FDA recommends that additional data collection be required for this first-of-a-kind device to assess longer-term safety and effectiveness clinical outcomes. The sponsor submitted proposals for two post-approval studies: extended follow-up of the OCS Liver PROTECT trial cohort; and extended follow-up of the OCS Liver CAP cohort. An overview of both PAS proposals is provided below, followed by the FDA's comments. FDA also believes that a new enrollment post-market trial is needed that addresses limitations of the premarket data. FDA seeks panel input on the need for, and design elements of a new enrollment PAS.

Extended Follow-up Studies of OCS Liver PROTECT and CAP Cohorts

Note: Due to similarities in the proposed extended follow-up studies of the OCS Liver PROTECT trial and OCS Liver CAP cohorts, these two PAS proposals are presented together in this section.

The sponsor proposes to continue follow-up of participants in the OCS Liver PROTECT trial (both OCS and Control arms) and in the OCS Liver CAP trial (OCS recipients only) up to 2 years post-transplant. The synopsis table below provides key trial design elements for these proposed post-approval studies:

Table 40. Key Trial Design Elements for Proposed Post-approval Studies

	Extended Follow-Up of PROTECT Trial Cohorts	
	PROTECT Trial	**CAP Trial**
Trial Objective	To evaluate long-term outcomes of OCS Liver recipients	
Trial Design	Observational trial of recipients who were enrolled and transplanted in the premarket studies	
Sample Size	300 recipients (OCS and Control arms combined)	Currently approved for enrollment of 74 OCS recipients
Primary Effectiveness Endpoint	Liver graft survival at 2 years post-transplant	
Other Clinical Endpoints	Recipient Survival at 2 years post-transplant	
Follow-Up Duration	2 years post-transplant	

FDA Comments:

1. FDA agrees with leveraging the premarket cohorts to obtain additional follow-up information, as this is a fast and efficient way to obtain and evaluate longer-term clinical outcomes. However, a key limitation of this approach is that potential bias introduced in the design and conduct of the PROTECT trial would persist in the extended follow-up studies.

2. In both PROTECT and CAP studies, recipients are already consented through 2 years of follow-up; therefore, this would be the most efficient way to learn about longer-term recipient outcomes following transplant with an OCS-perfused liver.

3. FDA continues to work with TransMedics to address concerns with the proposed post-approval data collection plans to ensure that if the device is approved, remaining questions about device performance will be sufficiently addressed.

New Enrollment Post-Approval Trial

In addition to the extended follow-up studies proposed by the sponsor, FDA believes that a new enrollment study is also needed to address questions and concerns that were raised in the PROTECT trial. A new PAS is needed to better understand the safety and effectiveness of the OCS device on DCD donor organs. Given that donor organ transplantability criteria were not validated in the PROTECT trial, a better understanding of transplantability criteria with respect to donor liver parameters and device-specific parameters is also needed. To address concerns regarding device malfunctions, we need high quality, prospective data collection on device malfunctions, conversion to cold storage, and organ turn-downs in order to further establish device safety in real-world use. FDA recommends a longer-term evaluation of clinically meaningful outcomes, such as recipient and/or graft survival post-transplant, with hypothesis testing. Lastly, the timing of randomization led to imbalances in the treatment arms, which may have biased the study results.

To address these concerns after device approval, FDA recommends that the new enrollment PAS be conducted as part of an existing post-market registry, the Thoracic Organ Perfusion (TOP) Registry, which is currently being used to fulfill post-market requirements for the OCS Lung System. TOP is an all-comers registry designed to collect real-world use data on every recipient who receives OCS-perfused lungs and every organ that comes into contact with the OCS device. Importantly, this registry collects data on organ turn-downs and conversion to cold storage. Most data are extracted from the UNOS database, but the TOP Registry also collects information that are not available in UNOS, including device-specific parameters, device malfunctions, and data on organ turn-downs. The TOP Registry also has built-in measures to minimize bias and ensure high quality data collection.

As mentioned above, the TOP Registry was designed to collect data on donor lungs perfused by the OCS system. However, given its strengths and accessibility, the TOP Registry may also be used for donor livers and serve as an infrastructure for collecting the sponsor's postmarket data on different donor organ types in a centralized location.

The panel will be asked to discuss the need for a post approval study, and if needed, important elements to include in the study.

10.0 Appendix 1 – Trial Screening Failures and Dry Runs

Initial PROTECT trial reports raised FDA concern regarding selection bias. These reports are summarized below.

- In the (b)(4) IDE supplement, the Sponsor provided data from the first 20 randomized and transplanted recipients that had reached 30 days of follow up. The PROTECT Trial, Part A report showed imbalances in donor/recipient baseline characteristics and higher number of screening failures (SFs) in the OCS arm (5/13, 38%) versus the Control (1/13, 8%) arm.

- The (b)(4) Annual Report (July 2016 through June 2017) included a data summary on 37 recipients (17 OCS and 20 Control recipients) enrolled and transplanted who reached 30 days follow-up post-transplantation. The imbalance on SF, observed in Part A, persisted in (b)(4) (24 SF in the OCS arm versus 1 SF in the Control arm). These early imbalances in screening failures raised FDA concerns regarding selection bias.

A screening failure was considered originally as a consented recipient matched with randomized donor liver, which eventually is not transplanted.

- In the (b)(4) Amendment, (Response to May 28, 2018 deficiency letter), the Sponsor communicated to the Agency that randomized screened subjects who were not transplanted and who returned to the waiting list awaiting for re-randomization, were not considered SF anymore and were removed from the original (b)(4) screening failure count. *(The Sponsor stated: "16 of the 25 screen failures are not categorized as screening failures anymore, because these recipients had returned to the waiting list awaiting re-randomization after at least one prior offer of donor liver deemed unsuitable for transplantation.)*

Despite the new SF definition, the SF imbalance across arms persisted (8 in the OCS arm versus 1 in the Control arm). FDA expressed their concerns to the Sponsor that potential selection bias would undermine the strength of the trial's data and render the data difficult to interpret.

- The 2018 annual report (b)(4) ; July 1, 2017 through December 12, 2018), showed that 211 recipients had been randomized, and 142 had been transplanted in the trial. The SF imbalance persisted, including 18 SF in the OCS arm in contrast to 7 SF in the Control arm. The presence of accessory vessels was the leading cause for screening failure in 12/18 (67%) in the OCS arm and 4/7 (57%) in the Control arm.

The sponsor acknowledged that they were aware of an imbalance in SFs across the two trial arms and stated: "We believe that a contributing factor to this imbalance is a lack of attention by the investigators to the presence *of accessory vessels in the livers randomized to the control group."*

- Amendment (b)(4) was submitted in response to the 2/8/19 Deficiency Letter for (b)(4) , which included the Agency's concerns for SF imbalances across arms and request to follow-up the outcomes of SF recipients who were withdrawn from the trial.

- The Annual Report (b)(4) , included a summary data of 217 enrolled recipients (107 OCS, 110 Control), who had been transplanted in the OCS Liver PROTECT Trial as of June 6, 2019. This accounted for two thirds of the target enrollment of 300 recipients. SFs were observed in 34 cases (all withdrawn after initial randomization and transplanted off trial). Dry Runs occurred in 57 cases (returned to waiting list (WL) and not considered SFs). Subsequently, 45/57 (79%), were withdrawal from the trial and only 12 remained in the WL until the end of the trial enrollment.

The current PMA (b)(4) report includes 300 enrolled recipients (OCS=153, Control=147). SF were observed in 129 WL recipients, and 176 liver donors. Donor SF were equally distributed; 88 cases in the OCS and 88 cases in the Control arms. Dry Runs (recipient back to WL) was observed in 130 (OCS=57, Control=73). SFs transplanted off trial after randomization were identified in 43 cases (OCS=28, Control=15).

Table 41. Change in Screening Failures (SFs) Incidence through Consecutive Annual Reports

January 24, 2016 through October 15, 2019	SF	
	OCS	**Control**
Part A report (b)(4) Enrollment: n=26 (OCS=13, Control=13)	5	1
Annual Report (b)(4) (July 2016 through June 2017) Enrollment: n=66	24	1
Amendment (b)(4) . Screening Failure Exclusions (Randomized Screened Recipients and not transplanted who returned to the waiting list awaiting for re-randomization, were not considered SF anymore and were removed from the original (b)(4) Annual Report screening failure count)	- 16	- 0
Annual Report Amendment (b)(4) (July 2016 through June 2017) Screening Failures Count After Exclusions Sixteen of the previous 24 screen failures in the OCS arm were not categorized as such anymore because those 16 recipients returned to the WL for re-randomization	24-16 =8	1-0 =1
Annual Report (b)(4) (July 1, 2017 through December 12, 2018) Enrollment: n=142 (OCS=71, Control =71) SF= 25 (All of them were withdrawn and transplanted off-trial) *142 have been transplanted in the trial*	18	7
(b)(4) Annual Report Amendment. Response to the 2-8-2019 Deficiency letter for (b)(4) Includes the 3 additional cases in the Control arm that were uncovered to have had accessory arteries based on the review of operative reports (*) and added as SF	18	7+3 =10***
Updated Report (b)(4) Response to 2/8/19 Deficiency Letter The Sponsor communicated of two additional control arm cases with accessory hepatic arteries were uncovered and added as SF	18	10+2 =12**

Annual Report (b)(4) Enrollment: n=217 (OCS=107, Control=110) Screening Failures, n=34 (All withdrawn after initial randomization and transplanted off trial) Dry Runs, n=57 (Returned to WL and not considered SF) Subsequently, 45 /57 (79%) were withdrawal from the trial and only 12 remained in the WL	22 (65%)	12 (35%)
Final PMA (b)(4) Report Enrolled and Tx, n=300 (OCS=153, Control=147). Screening Failures, n=129 WL recipients and 176 Donors		
Screening Failures after randomization, n=176 of 476 Screened Donors	88	88
Dry Runs: Rejected for transplantation in donor body after randomization – Recipient back to WL) n=130 (5)	57 (44%)	73 (56%)
Transplanted off trial after randomization using cold storage (Control) n=43	28	15
Rejected after assessment in the OCS system n=3	3	N/A

*These three cases should be considered "protocol Violations" and not considered as "Screening Failures"

** In (b)(4) , TransMedics identified the two additional donor screen failures in the Control group.

***(7 plus 3 cases more found in Operative Report Review (b)(4)

****Transplanted (Tx) Off Trial without Re-Randomization After Initial Donor Offer(s) were Declined for Tx at Retrieval (N=49: – N=25 – Subsequent donor liver offer did not meet OCS Liver PROTECT trial inclusion criteria. – N=21 – Site PI decided not to re-randomize recipients. – N=3 – Recipients no longer met trial eligibility criteria)

Table 42 Recipient Randomization and Screening Failures

	OCS	Control
Total Initial Consented WL Recipients n= 429	**214**	**215**
	Initial Randomization	
Screening Failures, n=129	61	68
WL Recipients Transplanted off trial n=92	51	41
WL Recipients Transplanted off trial without re-randomization and withdrawn after initial randomization, n=49* n=25 – Subsequent donor liver offer did not meet inclusion criteria n=21 – Site PI decided not to re-randomize at new donor offer n=3 – Recipients no longer met trial eligibility criteria	23	26
Recipients Transplanted off the trial after randomization, using Control n=43	28	15
n= 39 (24 OCS, 15 Control) – Donor liver did not meet eligibility due to accessory vessels, liver hematoma, or required surgical vascular repair.	24	15
n=4 logistical reasons	4	0
Dry runs resulted at donor final examination. The trial enrollment ended before these recipients received a donor liver transplant n= 26		
Remained alive on WL at time of enrollment conclusion n= 22		
Died on WL waiting for re-randomization n=4 Initial randomization?		
Recipient was delisted for transplant n=9	6	3
Recipient withdrawn consent n= 2	1	1

*In 21 cases (PI decided not to re-randomize recipients at donor offer due to donor OR logistical reasons or lack of trial trained retrieval staff at time of donor offer.

Table 43 Randomized Screened Donors and Screening Failures

	OCS	Control
Screened Donors n=475	240	235
Randomized n=302	155	147
Randomized but not transplanted n=4	3 instrumented and turned down	1 Death in the OR
Donor liver transplanted (mITT population) n=298	152	146
Screening Donor Failures after randomization n=176/475 (37%)	88	88
Rejected for transplantation in donor body after randomization (Dry Runs – Recipient back to WL) n=130	57/130 (44%)	73/130 (56%)

Clinical judgement at retrieval n=31	9	22
DCD donor did not expire within 30 mins n=42	18	24
Steatosis n=27	13	14
Cirrhosis or fibrosis of the donor liver n=9	3	6
Vasculature abnormalities or diseased n=4	2	2
Donor-recipient organ size mismatch n=3	3	0
Other reasons	14	5
Transplanted off trial after randomization using cold storage (Control)[1] n=43	28	15
Rejected after assessment in the OCS system[2] n=3	3 (DCD)	N/A

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

– N= 39 (24 OCS, 15 Control) – Donor liver did not meet eligibility due to accessory vessels, liver hematoma, or required surgical vascular repair.

– N= 4 (4 OCS, 0 Control) – Logistic reasons, including:

• Donor family not consenting to research (OPO requirement);

• 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.

2DCD Donors Rejected for Tx After OCS Liver Assessment N=3

– N=2 – Rising lactate levels despite maximizing OCS Liver perfusion parameters.

– N=1 – Donor liver pre-retrieval biopsy revealed extensive bridging fibrosis.

Table 43. Liver PROTECT Trial Screening Failures (WL Recipient Transplanted out of the Trial)

	OCS	Control
Total Initial Consented WL Recipients n= 429	214	215
	Initial Randomization	
Screening Failures n=129	61	68
SF WL Recipients Transplanted off trial n=92	51	41
Recipients Transplanted off trial after returned to WL and withdraw without re-randomization n=49*	23	26
Recipients Transplanted off the trial after first randomization, using Control n=43	28	15

Total Initial Consented WL recipients n= 429, 129 were considered SF.

* 2 recipients were deemed ineligible for the trial by the PI.

** In 21 cases (PI decided not to re-randomize recipients at donor offer due to donor OR logistical reasons or lack of trial trained retrieval staff at time of donor offer.

*** Consented and randomized WL recipients transplanted off trial using cold storage (Control) after randomization. N=43

The Sponsor's Ad Hoc analysis pulled together 30-day survival data in the ITT and mITT2 subjects population and 30-day survival data on 43 SF recipients withdrawn from the trial after initial randomization. These analyses left out 49 SF recipients initially randomized, who returned to WL, and subsequently transplanted out of trial without re-randomization. There were no recipient and graft survival differences between OCS and control for either the mITT2 or the ITT analysis.

11.0 Appendix 2 – Statistical Considerations

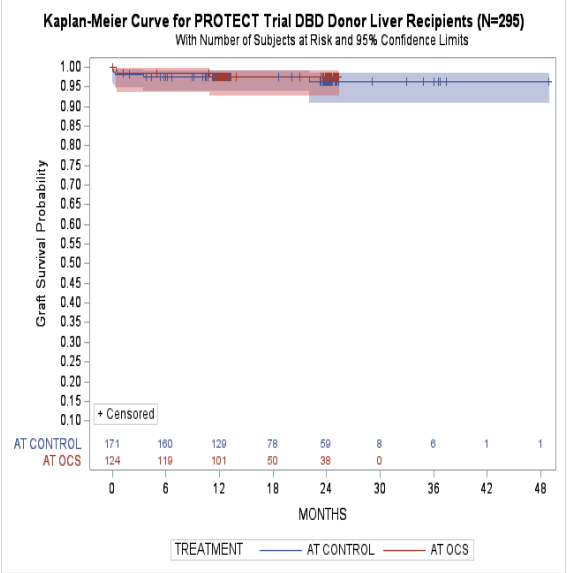
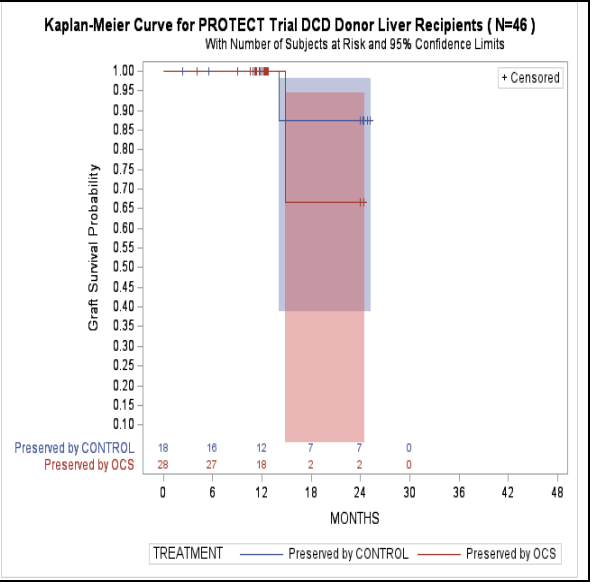
A. DBD and DCD subgroups, survival analysis

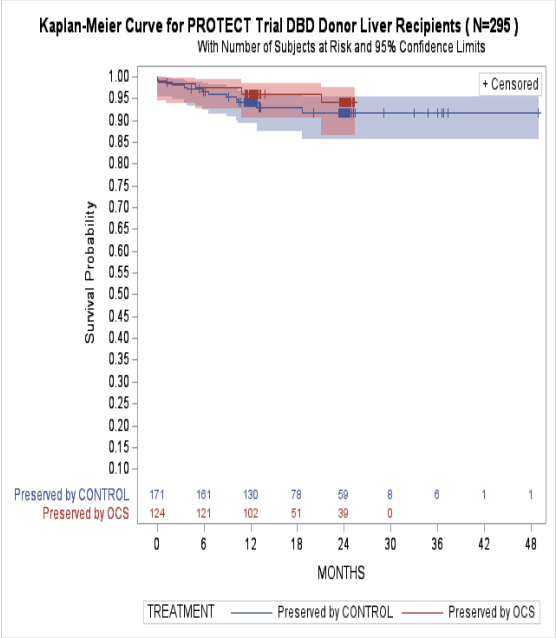
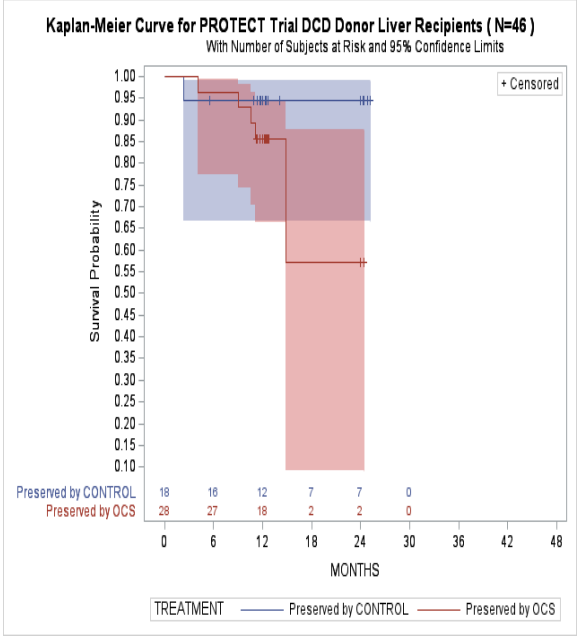
The PROTECT trial includes two distinct populations, DBD (N=296) and DCD (N=47) liver transplant recipients.

For DBD recipients, the Kaplan-Meier curves below show that the recipient survival and graft survival are similar in the OCS and the Control arms (observed differences about 1% at 6, 12, and 24 months as in Table 30, Section 6.5.10, DCD Liver Results).

For DCD recipient, the Kaplan-Meier curves show clear separation of recipient survival between OCS and Control: the observed difference shows 37% better recipient survival in the Control arm than in the OCS arm at 24 months. (The recipient survival rates are 96%, 86% and 57% at 6, 12, and 24 months for the OCS arm, and 94% for the Control arm at these follow-up times.) This difference corresponds to the 5 of 28 recipient deaths in the DCD OCS arm (1 of 18 in the DCD Control) shown in Table 30.

Figure 23. Graft Survival (Death Censored) and Recipient Survival in DBD and DCD Subgroups of the ITT Population for the OCS and Control arms

	DBD (n=295)	**DCD (n=46)**
Graft Survival		

Recipient Survival		

B. Propensity Score Analysis

Exploratory propensity score analysis was conducted by FDA to adjust for potential baseline imbalance between treatment arms in terms of five baseline covariates (steatotic liver (≤ 20%; >20%); DCD yes or no; donor age (<40; ≥40); recipient gender and recipient age). The propensity score is the probability of receiving the treatment rather than control, conditional on the observed covariates, and is a one-dimension summary of these observed covariates. The propensity score is estimated for each recipient, and then the estimated propensity scores are ordered and divided into five approximately equally sized subgroups (or strata) using the quintiles of the estimated propensity score. It is aiming to mimic a well-planned and conducted randomized controlled trial and "balance" the original baseline covariate distributions across the two treatment groups within propensity score strata.

The following table summarizes the point estimate of survival rate differences and their 2-sided 95% confidence intervals at Month 6, 12 and 24 after propensity score adjustment. A positive difference means a higher survival rate in the OCS arm. All the 95% CIs includes 0, lending support to the lack of clinical benefit in favor of OCS in terms of recipient survival and graft survival at 6-, 12-, and 24-month. This finding is consistent with the analysis without propensity score adjustment.

Table 44. Survival Analysis Results based on Propensity Score Analysis (N=343)

Time Points	**Graft Survival Difference (OCS-Control)**		**Recipient Survival Difference (OCS-Control)**	
	(%)	95% CI (%)	(%)	95% CI (%)
Month 6	-1.2	(-6.82, 4.49)	0.77	(-6.30, 7.84)
Month 12	-1.8	(-6.83, 3.31)	0.74	(-9.48, 10.96)
Month 24	-0.32	(-14.33, 13.69)	-1.80	(-16.27, 12.68)

12.0 Appendix 3 – Liver Biopsy Processing and Scoring Methods

As discussed in Section 6.5.7, Pathology Results, liver tissue samples were obtained from the OCS and Control arm recipients:

- pre-retrieval of the donor liver,
- post-preservation, and
- post-perfusion of the donor organ in the recipient.

The liver tissue samples were scored by a core Pathology laboratory at the (b) (6)

Parameter	Selection/Scoring Options
Portal Inflammation:	
Overall Severity	N/A, None, Minimal, Mild, Moderate, Severe
Inflammation distribution	Diffuse, Mostly Diffuse, Mostly Heterogenous, Very Heterogenous, N/A
Type of portal inflammation	Neutrophils, Eosinophils, Macrophage/monocyte, Lymphocytes, Plasma Cells, Granulomatous, N/A
Secondary Type of portal inflammation	Neutrophils, Eosinophils, Macrophage/monocyte, Lymphocytes, Plasma Cells, Granulomatous, N/A
Tertiary Type of portal inflammation	Neutrophils, Eosinophils, Macrophage/monocyte, Lymphocytes, Plasma Cells, Granulomatous, N/A
Lobular Necrosis:	
Overall Lobular Necrosis severity	Overall Lobular Necrosis Severity, None, Mild, Mod, Sev, N/A
Lobular Necrosis Type	Lobular Necrosis Type, Spotty, Confluent, Other, N/A
Lobular Necrosis Primary location	Lobular Necrosis location, Periportal, Midzonal, Perivenular, Panlobular or N/A
Lobular Necrosis secondary location	Lobular Necrosis location, Periportal, Midzonal, Perivenular, Panlobular or N/A
Lobular Necrosis tertiary location	Lobular Necrosis location, Periportal, Midzonal, Perivenular, Panlobular or N/A
Lobular Inflammation:	
Overall Lobular Inflammation	Overall Lobular Inflammation Severity, None, Mild, Mod, Sev, N/A
Lobular Inflammation primary location	Lobular Inflammation location, Periportal, Midzonal, Perivenular, Panlobular or N/A
Lobular Inflammation secondary location	Lobular Inflammation location, Periportal, Midzonal, Perivenular, Panlobular or N/A
Primary Type of lobular inflammation	Neutrophils, Eosinophils, Macrophage/monocyte, Lymphocytes, Plasma Cells, Granulomatous, NA

Secondary type of lobular inflammation	Neutrophils, Eosinophils, Macrophage/monocyte, Lymphocytes, Plasma Cells, Granulomatous, NA

Parameter	**Selection/Scoring Options**
Tertiary Type of lobular inflammation	Neutrophils, Eosinophils, Macrophage/monocyte, Lymphocytes, Plasma Cells, Granulomatous, NA
Lobular Steatosis:	
Severity of macro lobular steatosis present in biopsy	measure to nearest 10% of macro lobular steatosis present in biopsy (e.g., 30)
Severity of micro lobular steatosis present in biopsy	None, Mild, Mod, Sev, N/A
Distribution of Macrovesicular steatosis	Periportal, Midzonal, Perivenular, Panlobular, NA
Distribution of Microvesicular steatosis	Periportal, Midzonal, Perivenular, Panlobular, NA
Liver Sinusoidal Endothelial Cell Evaluation:	
Liver Sinusoidal Endothelial Cell coverage	Estimated to nearest 10 percent (e.g., 30)
Primary LSEC loss	Periportal, Midzonal, Perivenular, Panlobular, NA
Secondary LSEC loss	Periportal, Midzonal, Perivenular, Panlobular, NA
Surface epithelial loss	0: no loss; 1: <= 50%, 2: > 50%
Liver Fibrosis:	
Portal Fibrosis scoring	None, Minimal, Mild, Moderate, Severe, N/A
Perivenular Fibrosis scoring	None, Minimal, Mild, Moderate, Severe, N/A
Central Venous Fibrosis scoring	None, Minimal, Mild, Moderate, Severe, N/A
Extra-hepatic Bile Duct Scoring:	
Intra-mural Bleeding	0: none; 1: <= 50%, 2: > 50%
Thrombi Lesions	0: No Thrombi, 1: Thrombi present
Vascular lesions	0: none, 1 <= 50% vessels, 2: > 50% vessels
Arteriolonecrosis	0: none, 1 <= 50% vessels, 2: > 50% vessels
Duct Necrosis	0: none, 1: < 25%, 2: 25-50%, 3: 50-75%, 4: > 75%
Inflammation	0: none, 1: at least > 10 leukocytes/HPF, 2: > 50/HPF
Sl gland injury	0: none, 1: <= 50%, 2: > 50%

Deep gland injury	0: none, 1: <= 50%, 2: > 50%
Diagnosis (and specimen comparison when applicable):	
Assessment of changes since previous biopsy timepoint	N/A or Minimal, Mild, Moderate Increase / Decrease
Parameter	**Selection/Scoring Options**
Primary Diagnosis	N/A, Minimal to no preservation/reperfusion injury (= 0), Mild preservation/reperfusion injury (= 0.25), Moderate preservation/reperfusion injury (= 1), Severe preservation / reperfusion injury, Other
Secondary Diagnosis	N/A, Minimal to no preservation / reperfusion injury, Mild preservation / reperfusion injury, Moderate preservation / reperfusion injury, Severe preservation / reperfusion injury, Other
Overall Case Score	Final composite score, range is from 0 to 3 (0 representing No Composite Damage, 3 Representing Severe Composite Damage)

13.0 References

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