SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Organ Preservation System

Device Trade Name: OrganOx *metra*® System

Device Procode: QQK

Applicant's Name and Address: OrganOx, Limited
Oxford Science Park
Magdalen Centre
Robert Robinson Avenue
Oxford OX4 4GA, UK

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P200035

Date of FDA Notice of Approval: 12/9/2021

II. INDICATIONS FOR USE

The OrganOx *metra*® is a transportable device intended to be used to sustain donor livers destined for transplantation in a functioning state for a total preservation time of up to 12 hours.

The OrganOx *metra*® device is suitable for liver grafts from donors after brain death (DBD), or liver grafts from donors after circulatory death (DCD) ≤40 years old, with ≤20 mins of functional warm ischemic time (time from donor systolic blood pressure <50 mmHg), and macrosteatosis ≤15%, in a near-physiologic, normothermic and functioning state intended for a potential transplant recipient.

III. CONTRAINDICATIONS

The OrganOx *metra*® should not be used for:

A. Living donor liver

B. Liver intended for split transplant

C. Recipients requiring all of the following at the time of transplantation:
- Oxygen therapy via a ventilator/respirator
- Inotropic support
- Renal replacement therapy
- Acute/fulminant liver failure (UNOS status 1A)
- Simultaneous organ transplantation

IV. WARNINGS AND PRECAUTIONS

A device malfunction or user error could lead to loss of a donor organ. Only trained and certified users should use the OrganOx *metra*® with the continuous support from OrganOx.

The complete list of warnings and precautions can be found in the Organ Ox *metra*® System labeling.

V. DEVICE DESCRIPTION

A. Overview of the Device System

The OrganOx *metra*® is a transportable device for sustaining donor livers outside the body in a near-physiologic, normothermic, and perfused state. It is intended to be used to transport donor livers destined for transplantation and can sustain them for periods up to 12 hours.

The device is comprised of three main components as described below:

OrganOx *metra*® Retained Unit: This is an electromechanical device that incorporates a centrigufal pump, oxygen concentrator, heat exchanger, and blood gas analyzer. These subassemblies are largely independent, but cooperate with each other under software control and are contained in the base unit.

OrganOx *metra*® Liver Perfusion Circuit (Disposable Set): The disposable set is a sterile, single-use perfusion circuit that maintains livers in a physiologic environment and has embedded sensors to control and monitor the perfusion parameters and bile production.

OrganOx *metra*® Sodium Taurocholate: Sodium Taurocholate is infused into the circulating perfusate to replenish bile salt levels during *ex-vivo* perfusion on the OrganOx *metra*®.

The OrganOx *metra*® is shown in **Figure 1**.

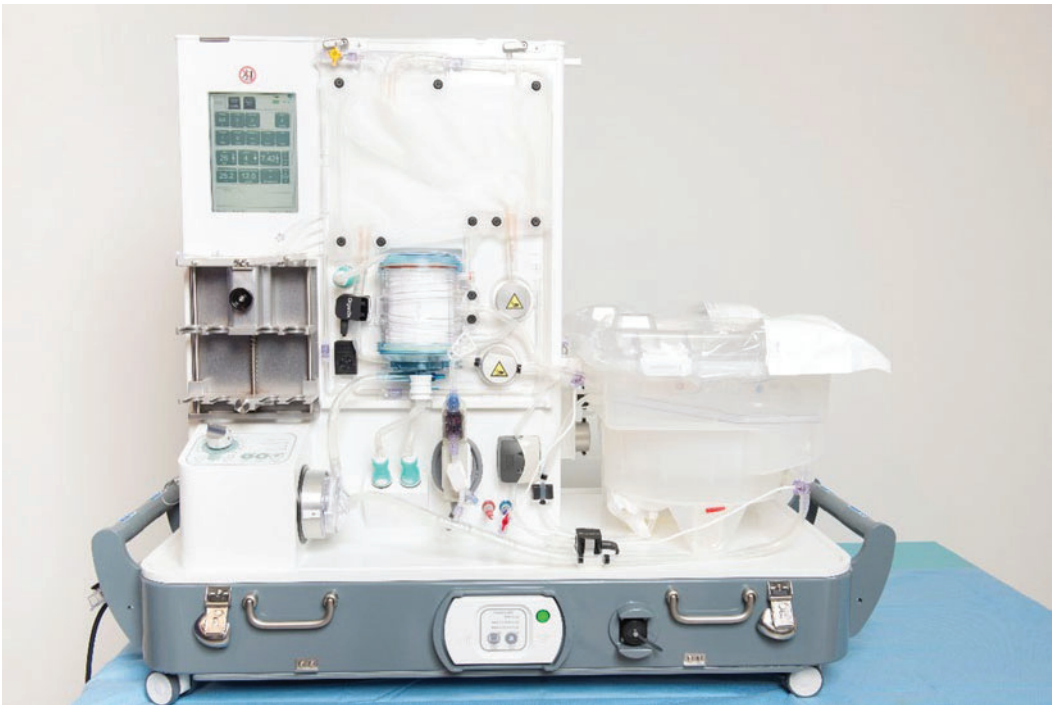

Figure 1: Components of the OrganOx metra® System. The figure shows the Liver Perfusion Circuit (Disposable Set) mounted on the Retained Unit

The OrganOx *metra*® Liver Perfusion Circuit Pack is used with the Retained Unit of the OrganOx *metra*® and contains all the disposables required for one liver perfusion. The OrganOx *metra*® Liver Perfusion Circuit Pack is supplied as a single-use device that has been sterilized by Ethylene Oxide by a subcontractor to OrganOx Ltd. and is connected to the device prior to the retrieval team accepting the organ. Venous blood exits the liver through the inferior vena cava (IVC) cannula and enters it through the arterial and portal cannulas. Excess blood is stored in the reservoir.

Arterial and IVC pressures are directly measured and controlled; the rotation speed of the centrifugal pump and the degree of construction of the proportional pinch valve are adjusted in tandem until the IVC pressure falls within the range of -1 to 2 mmHg and the arterial pressure is in the range of 60-75 mmHg. Portal pressure is not controlled, and blood flows into the portal cannula from the reservoir under the effect of gravity. Both IVC and portal flows are directly measured, but not controlled; the portal flow sensor simultaneously functions as both a bubble detector and triggers an immediate shutdown of the portal pinch valve if air is detected to prevent air entrainment into the liver.

During liver perfusion, blood passes through a combined oxygenator and heat exchanger. Based on inline measurements of partial pressure of oxygen, carbon dioxide, and temperature obtained by means of an integrated blood gas analyzer, the ratio of oxygen to air gas influx and inlet water temperature to the oxygenator are adjusted to maintain pO2 in the range of 12-18 kPa, pCO2 in the range of 4-7 kPa, and temperature at 37°C. During perfusion, the liver will normally “sweat” ascites and produce bile via the biliary duct.

Ascites can drain into the liver bowl through a perforated liver sling; the level of ascites in the bowl is automatically sensed via a level switch. When ascites within the collection bowl exceeds a predetermined level, a roller pump is activated, which returns ascites to the reservoir to maintain a constant perfusate volume. The throughput of bile excreted via the bile cannula is discarded and stored in a separate bile sump compartment within the liver bowl.

To maintain cellular metabolism, the liver receives nutrition via a roller pump and insulin through the syringe pump. Insulin is infused at a constant rate whilst the nutrition pump is started once when the glucose falls below a threshold in accordance with the last glucose value entered by the user. Heparin, prostacyclin and bile salts are infused at a constant rate via the syringe driver pump in order to prevent clotting, provide vasodilation, and assist with bile production. The principle of the design of the OrganOx metra® is detailed in **Figure 2**.

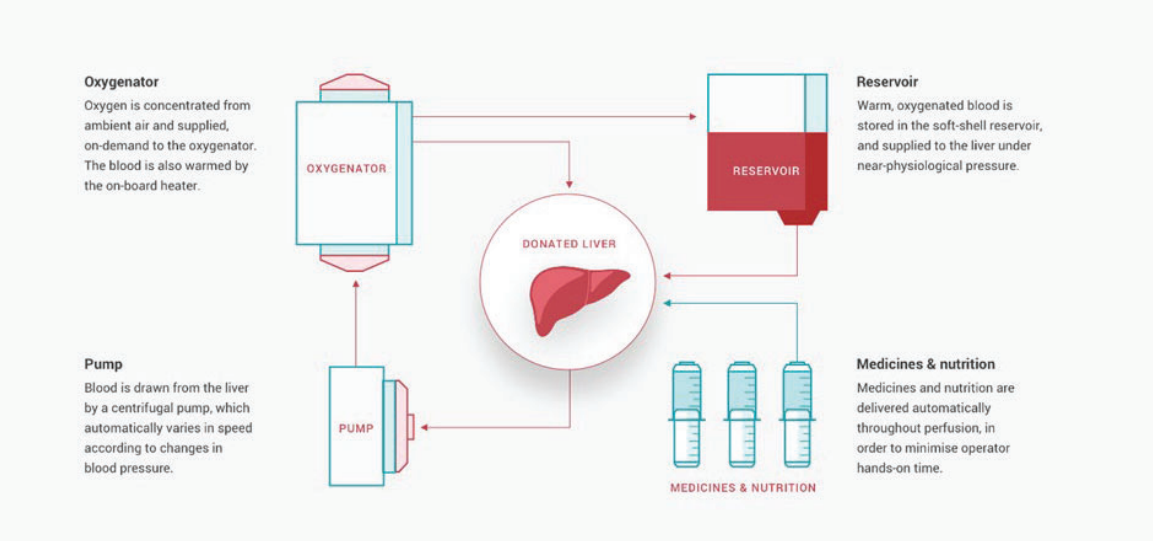

Figure 2: OrganOx *metra*® principles of operation

B. Retained Unit (Product Code D0003)

The reusable base unit implements a software-control algorithm that controls the perfusion function and allows for monitoring and adjustment of perfusion parameters. The device provides users with quantitative data acquired during perfusion, including:

- Arterial and IVC pressures
- Portal, arterial, and IVC flow rates
- pO2, pCO2, and pH
- Blood temperature
- Glucose reading (latest manual input and time of manual input)
- Bile production
- Organ perfusion time

- System status information, warning messages, and alarms

C. Disposable Set (Product Code D0146)

The Disposable Set used with the Retained Unit of the OrganOx *metra*® contains all the disposables required for organ perfusion. This includes:

- A sterile tubing set containing a blood reservoir, perfusion lines, a blood oxygenator, centrifugal pump head, flow sensors, and pressure sensors
- A sterile organ storage bowl (also called Liver Bowl), which is preconnected to the tubing set described above to retain the organ while on the device
- Sterile cannulas for the hepatic artery, portal vein, and inferior vena cava with easy connection attachment to the perfusion circuit
- Blood gas sensors for monitoring pO2, pCO2, and pH by means of online blood gas analysis
- Sodium Taurocholate, provided as a sterile, lyophilized powder (see section below)

D. Perfusion Solutions

Note: All solutions required for the operation of the metra® (apart from the Sodium Taurocholate) are routinely available and are not supplied as part of the metra® device.

Sodium Taurocholate (Product Code C0364) is manufactured from cholic acid and is provided as component of the Disposable Set. It is a nature-equivalent compound, chemically identical to the natural compound produced in the liver of many animal species.

The perfusion solutions include bolus injections (given at the start of perfusion) and the maintenance infusions (given throughout perfusion).

Before connection of the liver, the blood based perfusate is supplemented with:

- Antibiotic to minimize risk of infection
- Anticoagulant to prevent thrombosis in the circuit
- Sodium bicarbonate (buffer) for adjusting the pH of the perfusate before the liver is placed on the device

- Calcium gluconate to correct the binding of citrate to calcium

During the perfusion the following are infused at a constant rate:

- Parenteral nutrition solution (a source of amino acids and glucose for liver maintenance)
- Insulin to control the perfusate glucose level
- Anticoagulant to prevent coagulation
- Epoprostenol (prostacyclin) to optimize microperfusion
- Sodium taurocholate (bile salts) to maintain appropriate bile production

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Liver transplantation is a treatment for end stage liver disease. There are multiple options for preservation of liver grafts prior to transplantation, including static cold storage (SCS) and normothermic machine perfusion (NMP).

Static Cold Storage
The current standard of donor liver preservation is based on static cold storage. During SCS, organs are flushed and cooled with specific chilled preservation solutions. After retrieval, the organ is placed in sterile plastic bags filled with preservation solution for transportation and stored in a cooler until transplantation. Hypothermia reduces the liver's metabolic activity, and the preservation solution minimizes the cellular swelling that otherwise occurs.

Normothermic Machine Perfusion
NMP is another donor liver preservation technique allowing for the *ex-vivo* maintenance of organs at body temperature. During NMP, oxygen and nutrients are provided to the liver and a blood-based perfusate is pumped through the organ under physiological rates of pressure and flow.

There is currently one US-marketed device indicated for the normothermic machine perfusion of donor liver grafts. The Food and Drug Administration approved the Organ Care System (OCS™) Liver device by TransMedics, Inc. on September 28, 2021, via P200031. The TransMedics® Organ Care System (OCS™) Liver is a portable extracorporeal liver perfusion and monitoring system indicated for preservation and monitoring of hemodynamics and metabolic function, which allows for *ex-vivo* assessment of liver allografts from donors after brain death (DBD) or liver allografts from donors after circulatory death (DCD) ≤ 40 years old and with ≤ 20 mins functional warm ischemic time,

macrosteatosis ≤ 15%, in a near-physiologic, normothermic and functioning state intended for a potential transplant recipient.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The OrganOx *metra*® System received full CE marketing approval from the European Union (including the UK) in December 2018.

The OrganOx *metra*® System is not marketed in the United States or any other foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

There is no direct patient contact when this device is used as labeled; however, the device has direct contact with the liver that is subsequently transplanted into a recipient. The donor liver quality and optimization after preservation have direct effects on allograft function and survival. As such, device misuse or malfunction may result in conversion to SCS with extra organ manipulation, potential for contamination, and prolonged warm and cold ischemic time, leading to graft injury or graft loss.

Below is a list of the potential adverse effects (e.g., complications) associated with liver transplants:

- Abdominal wound dehiscence
- Acute rejection
- Anastomotic site complications; narrowing, bleeding or occlusion
- Anemia
- Ascites
- Aspiration
- Atrial fibrillation
- Biliary strictures and bile leaks
- Bleeding
- Bowel obstruction
- Bowel thromboembolic complications and gangrene
- Cerebrovascular accident
- Cholangitis
- Coagulopathy
- Convulsion
- Death
- Delirium, confusion and neurological complications
- Diaphragmatic injury
- Drug Toxicity
- Early liver allograft dysfunction (EAD)
- Fever
- Gastritis
- Gastro esophageal reflux disease (GERD)
- GI Bleeding (upper or lower)
- Hemodynamic instability
- Hepatic artery thrombosis

- Hepatic coma
- Hepatic psychosis
- Hyperacute rejection
- Hyperammonemia
- Ileus
- Liver abscess
- Liver primary non-function
- Malignancy
- Multiple organ failure
- Pancreatitis
- Peptic ulceration
- Phrenic nerve injury
- Pleural effusion
- Portal vein thrombosis
- Protamine and other anti-heparin medication reaction
- Renal dysfunction and/or failure
- Respiratory failure
- Sepsis
- Stroke
- Transfusion reaction
- Venous thromboembolism (deep venous thrombosis [DVT])
- Wound Infection

For the specific adverse events that occurred in the US clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

OrganOx conducted the following nonclinical studies to evaluate the OrganOx *metra*®: engineering bench testing, biocompatibility and biological safety, software verification and validation, cybersecurity, electrical and medical device safety, electromagnetic compatibility, sterilization, shelf-life, and animal functional testing.

A. Sodium Taurocholate Testing

A summary of the non-clinical laboratory testing performed on the sodium taurocholate solution is provided in **Table 1** below:

Table 1: Sodium Taurocholate Testing Summary

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/Significant Deviations	Results
Dose Verification	10 products	ISO 11137-2	8.2 kDy±10% ≤ 1 positive sterility test	None	Pass
Bacteriostasis/ Fungistasis	5 products	Direct inoculation	Positive growth at 5 days	None	Pass
Dose Mapping	1 packed shipper	ISO 11137-2	25 kGy minimum	None	Pass
Dose Audit August 2017	10 products	ISO 11137-2	8.2 kDy±10% ≤ 1 positive sterility test	None	Pass
Dose Audit June 2018	10 products	ISO 11137-2	8.2 kDy±10% ≤ 1 positive sterility test	None	Pass
Impact of Irradiation FTIR	1 batch irradiated; 1 batch non irradiated	FTIR internal method	Comparable FTIR spectra	None	Pass
Impact of Irradiation HPLC	1 sample irradiated; 1 sample non irradiated	HPLC internal method	Comparable HPLC trace and concentration	Slight increase in concentration but samples not weighed	Pass (FTIR)

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/Significant Deviations	Results
Impact of Irradiation HPLC Additional Study	3 samples irradiated; 1 sample non irradiated	HPLC internal method	Comparable HPLC trace and concentration	None	Pass
Chemical Characterization	3 samples; glass vial (50 mL) and rubber stopper	ISO 10993-18	No significant leachable substances	None	Pass
Heavy Metals Perfusate Solution at 24 hours	2 samples of perfusate solution	AAS ISO 15747	≤maximum permissible concentration	Aluminum at maximum limit of 0.05	Pass
Bacterial Endotoxin	3 batches	Turbidimetric kinetic method	<0.5EU/ml	None	Pass
Sodium and Calcium Concentration Perfusate Solution at 24 Hours	5 samples perfusate solution T=0 to T=4	Ion Chromatography (IC)	No clinically significant changes over 24 hours	51% decrease in calcium ion concentration	Pass
Stability Perfusate Solution at 48 Hours	6 samples perfusate solution T=0 to T=5	HPLC internal method	No significant new peaks	None	Pass
Shelf Life of Sodium Taurocholate (Accelerated)	1 batch stored at 40°C 90% RH	Concentration HPLC Moisture content (mass loss/gain)	For information only ≤10% change	12.5% in concentration Storage range is: 15°C to 25°C	Pass
Shelf Life of Sodium Taurocholate (Real Time)	1 batch stored at 25°C	Concentration HPLC Moisture content (mass loss/gain)	For information only ≤10% change	None	Pass

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/Significant Deviations	Results
Packaging Seal Integrity Dye Penetration	36 pouches	ASTM F3039-15	No Leaks	None	Pass
Packaging Seal Integrity Burst Strength	34 pouches	ASTM F1140-07	Minimum 139 mbar	None	Pass
Viral Safety Report	Validation of scale down: 3 batches Inactivation studies: 1 sample per model virus and timepoint	ISO 22442-3	Overall reduction of 6 log	Additional testing done to confirm antiviral activity of bile starting material	Pass

B. <u>Disposable Set Testing</u>

A summary of the non-clinical laboratory testing performed on the Disposable Set is provided in **Table 2** below:

Table 2: Disposable Set Testing Summary

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/Significant Deviations	Results
Equivalence of Sterilization Chambers	Full load per chamber half cycle	ISO 11135	PPQ: cycle parameters meet specification; MPQ: no positives	None	Pass
Sterilization MPQ	Reference loads 3 half cycles	ISO 11135 AnnexB.1.2a	No positive BI or PCDs	None	Pass
Sterilization PPQ	1 Full cycle	ISO 11135 AnnexB.1.2a	Cycle parameters meet specification	None	Pass
Sublethal Comparison	3 samples of Cold Liver	ISO 11135	CFU count: product < PCD	None	Pass

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/Significant Deviations	Results
	Perfusion Pack 3 PCDs				
Resistance Comparison	3 samples Cold liver perfusion pack 3 PCDs	ISO 11135	Resistance PCD ≥ product	None	Pass
EO Residuals	1 sample each pack per time point	ISO 10993-7	≤ 4 mg/device: Surgeons Pack Liver Perfusion Set ≤ 21mg/device: Perfusionist Pack	None	Pass
Ethylene Chlorohydrin (ECH) Residuals	1 sample each pack per time point	ISO 10993-7	≤ 9 mg/device:	None	Pass
Bacterial Endotoxin	1 sample per pack/part of pack tested in duplicate	Turbidimetric kinetic method	20 EU/sample	None	Pass
Bacterial Endotoxin	1 disposable set and full perfusion of perfusion solution	Turbidimetric kinetic method	<20 EU/sample	None	Pass
Shelf Life Visual	18 units each time point and condition	Internal method	Seals intact No significant damage to set	Minor damage and discoloration	Pass
Shelf Life Seal Integrity (Peel Strength)	18 units each time point and condition	ASTM F88-15	Maximum peel force at N15mm	None	Pass

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/Significant Deviations	Results
Shelf Life Dye Penetration	18 units each time point and condition	ASTM F1929-15 ASTM F3039-15	No leaks	None	Pass
Shelf Life Functional	18 units each time point and condition	Internal method	No persistent leakage	None	Pass
Cytotoxicity	1 disposable set	ISO 10993-5: L929 MEM Elution	< grade 2	None	Pass
Sensitization	1 disposable set	ISO 10993-10: Guinea Pig maximization	No evidence of sensitization	None	Pass
Irritation	1 disposable set	ISO 10993-10: Intracutaneous Reactivity	No erythema or edema	None	Pass
Acute Systemic Toxicity	1 disposable set	ISO 10993-11	No evidence of significant systemic toxicity or mortality	None	Pass
Pyrogenicity	1 disposable set	ISO 10993-11: Rabbit	Non-pyrogenic	None	Pass
Leachables (at 24 Hours)	3 Disposables Sets	HPLC internal method	No significant leachable substances	None	Pass
Heavy Metals Perfusate Solution (at 24 Hours)	2 samples perfusate solution	AAS ISO 15747	≤maximum permissible concentration	Aluminum at maximum limit of 0.05	Pass
Sodium and Calcium Concentration Perfusate Solution at 24 Hours	5 samples perfusate solution T=0 to T=4	IC	No clinically significant changes over 24 hours	51% decrease in calcium ion concentration	Pass

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/Significant Deviations	Results
Cytotoxicity (With perfusion solutions)	1 disposable set and full perfusion of perfusion solution	ISO 10993-5 L929 MEM Elution	< grade 2	None	Pass
Sensitization (With perfusion solutions)	1 disposable set and full perfusion of perfusion solution	ISO 10993-10 Guinea Pig maximization	No evidence of sensitization	None	Pass
Irritation (With perfusion solutions)	1 disposable set and full perfusion of perfusion solution	ISO 10993-10 Intracutaneous Reactivity	No erythema or edema	None	Pass
Acute Systemic Toxicity (With perfusion solutions)	1 disposable set and full perfusion of perfusion solution	ISO 10993-11	No evidence of significant systemic toxicity or mortality	None	Pass
Pyrogenicity (With perfusion solutions)	1 disposable set and full perfusion of perfusion solution	ISO 10993-11 Rabbit	Non-pyrogenic	None	Pass
Seal Integrity	179 Disposable sets	ASTM F1929-15 Method A	No signs of leak	None	Pass
Post-Aging functional testing	179 Disposable sets	ISTA 3E, ASTM F1929-15, ASTM F3030/ASTM F88-15)	No signs of leak	None	Pass
Sealing Validation	60 Header bags	ISO 11607	Lower limit of tolerance >14 N/15 mm	None	Pass

C. OrganOx *metra*® System Testing

The OrganOx *metra*® was tested to demonstrate that it meets requirements for medical device safety, including electrical safety. The system was tested by an outside laboratory according to the IEC 60601-1 (Edition 3.1) and 60601-1-2:2014 (EMC; Edition 4) standards, as well as the ANSI/AAMI and CSA version of the standard.

A summary of the non-clinical testing performed on the Retained Unit is provided in **Table 3** and *metra*® system in **Table 4** below:

Table 3: Retained Unit Testing Summary

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/ Significant Deviations	Results
Emissions Test	1 Device	EN61000-3-2:2006 + A2:2009	Class A	None	Class A
Radiated Emissions	1 Device	EN55011:2009 + A1:2010	Class A	None	Class A
Conducted Emissions	1 Device	EN55011:2009 + A1:2010	Class A	None	Class A
Conducted Emissions – Line Impedance Stabilization Network	1 Device	EN55022:2010 using CISPR 25 EN 301489	Class A	None	Class A
Mains Harmonic Emissions	1 Device	EN61000-3-2:2006 + A2:2009	Class A	None	Class A
Mains Voltage Fluctuations and Flicker	1 Device	EN61000-3-3:2013	Complies	None	Complies
Emissions Test	1 Device	CFR 47 Part 15.107 and 15.109	Class A	None	Class A
Electrostatic Discharge (ESD)	1 Device	EN61000-4-2:2009	±8 kV – contact discharge ± 15 kV – air discharge	None	Complies
Radiated Immunity	1 Device	EN61000-4-3:2006+A2:2010	3 V/m 80 MHz–2.7 GHz –Frequency range 10 V/m –voltage	None	Complies
Electrical Fast Transient/Burst	1 Device	EN61000-4-4:2012	+2kV for input/output lines	None	Complies
Surge	1 Device	IEC61000-4-5:2006	±2kV for Common mode	None	Complies

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/ Significant Deviations	Results
			±1kV for Differential mode		
Immunity to Electromagnetic Disturbances Caused by Radio Frequency Disturbances Testing	1 Device	EN61000-4-6:2009	3 Vrms 150 kHz – 80 MHz	None	Complies
Power Frequency (50/60 Hz) Magnetic Field	1 Device	EN61000-4-8:2010	30 A/m	None	Complies
Voltage Dips, Short Interruptions and Voltage Variations on Power Supply Input Lines	1 Device	EN61000-4-11:2004	100% reduction for 10 ms/half cycle 30% reduction for 500 ms/25 cycles 100% reduction for 20 ms/1 cycle 100% interruption for 5 s	None	Complies
Conducted Transient Immunity	1 Device	ISO 7637-2:2011	Pulse severity level I/II	None	Complies
Conducted Transient Emissions	1 Device	ISO 7637-2:2011	LISN 5 µH/50 Ω	None	Complies
Basic Electrical Safety	1 Device	IEC 60601-1:2005 + CORR. 1 2006 + CORR. 2:2007 + AM1:2012	Compliant to Relevant clauses	None	Complies
Device Alarms	1 Device	IEC 60601-1-8:2006 + Am. 1:2012	Equipment includes alarm systems complying with collateral standard	None	Complies

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/ Significant Deviations	Results
			as means of risk control to have equipment notify the operator of a hazardous situation. In line with clauses 4, 5.1, 5.2.1, 6.1.1, 6.1.2, 6.2, 6.3.1, 6.3.2, 6.3.3, 6.4, 6.4.1, 6.4.2, 6.5.1, 6.5.2, 6.5.3.1, 6.5.3.2, 6.5.4.1, 6.5.4.2, 6.5.5, 6.6.1, 6.7, 6.8.1, 6.8.2, 6.8.3, 6.8.4, 6.8.5, 6.9, 6.10, 6.11.1, 6.12		
Usability Engineering	1 Device	IEC 60601-1-6:2010 ISO 62366:2007	Usability engineering process complies with IEC 62366	None	Complies
Environmental	1 Device	EN 60068-2-1:2007 Cold EN 60068-2-2:2007 Dry Heat EN 60068-2-6:2008 Vibration (sine) EN 60068-2-14:2009 Temperature Change EN 60068-2-78:2002 Damp Heat EN 60601-1:2006/A1:2013 non UKAS	30°C for 4 hours 28°C 93% RH for 7 days -5°C for 16 hours +55°C for 16 hours 0°C for 2 hours +40°C for 2 hours -5°C for 20 minutes	None	Pass with respect to all acceptance criteria

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/ Significant Deviations	Results
Environmental	1 Device	EN 60068-2-64:2008 Vibration Random	10-57 Hz at 0.15mm 57-150 Hz at 2g	None	Failed, but complies with device operational specification
Environmental	1 Device	EN 1789:2007 + A1:2010 non UKAS	10-20 Hz at 0.05 g2/Hz 20-150 Hz at -3 db/octave	None	Failed but complies with device operational specification
Secondary cells and batteries containing alkaline or other non-acid electrolytes – safety requirements for portable sealed secondary cells	36 battery cells	ISO 62133:2002	Compliant with clauses: 1, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 3.0, 4.0, 4.1, 4.2.2, 4.2.3, 4.2.4, 4.3, 4.3.2, 4.3.3, 4.3.4, 4.3.8, 6.2, 6.3, 7.0	None	Complies
Electromagnetic Compatibility – Emissions and Immunity	1 Device	IEC 60601-1-2:2014	Continuous phenomena – radiated RF immunity, conducted RF immunity, power frequency magnetic field immunity Liver On Board Mode Transient phenomena – ESD, electrical fast burst transient immunity, surge immunity, power line voltage dips and interrupts	None	Pass
ElectroMagnetic Compatibility (EMC) standard for radio equipment and services; Part 17: Specific conditions for Broadband Data Transmission Systems; Harmonised Standard covering the essential requirements of article 3.1(b) of Directive 2014/53/EU	1 Device	ESTI EN 301 489-17		None	Complies

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/ Significant Deviations	Results
			Liver On Board Mode and Preparation Mode		
Electromagnetic compatibility and Radio spectrum Matters (ERM); ElectroMagnetic Compatibility (EMC) standard for radio equipment and services; Part 1: Common technical requirements	1 Device	ESTI EN 301 489-1		None	Complies
Electromagnetic compatibility (EMC) - Product family standard for aftermarket electronic equipment in vehicles	1 Device	EN 50498:2011		None	Complies
Ingress Protection	1 Device	IEC 60529:1992 + A2:2013	IP44 Cover removed	None	Pass
Powerbase Requirements	1 Device	Internal Method	Current path switching hierarchy: 1. Mains PSU 2. External DC input 3. Internal Batteries Current path switching time: <5ms with no loss of machine performance Battery charging voltage: 36VDC max 2 channels	None	

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/ Significant Deviations	Results
			Battery charging current: 3Amps max, constant current, 2 channels M12 isolated voltage output: 12VDC +/-10% M12 current: 0.8Amps max M12 isolation >4kV RMS Digital I/O To interface board: Power status Keypad inputs From interface board: Keypad LEDs Cooling fan enabled		
Backplane requirements	1 Device	Internal Method	Passive printed circuit board for interconnection and routing of signal and power for the following: DC board Interface board Master control board Trinamics carrier board Ancillary component (cooling fans, pumps, stepper motors, blood gas analyzer, thermal control unit,	None	

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/ Significant Deviations	Results
			oxygen concentrator control module)		
Interface board requirements	1 Device	Internal Method	Integrate flow sensor electronics: EMTEK flow sensor daughter boards, 2 channels Serial communication protocols: RS485 to/from master control board RS232 to/from battery modules SPI to/from trinamics carrier and flow sensors I2C for digital I/O expander Processor: AT91SAM7 Power Rails: Digital Rail1 voltage: 3.3VDC +/-5% Digital Rail1 current: 1Amp max Digital Rail2 voltage: 5VDC +/-5% Digital Rail2 current: 0.12Amps max 12VPeripheral voltage: 12VDC +/-10%	None	

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/ Significant Deviations	Results
			12V Peripheral current: 3.2Amps minimum 24VPeripheral voltage: 24VDC +/- 10% 24VPeripheral current: 1.2Amps minimum Digital I/O: Button press and status LEDs		
Master control board requirements	1 Device	Internal Method	Integrate the following processor board: UCB+ V1.2 - Surface Measurement Systems Processor: AT91SAM7 Rail voltages: Input supply voltage: 12 VDC +/- 8% Input supply current: 0.6 Amps max Digital 5V voltage: 5 VDC +/-5% Digital 5V current: 1 A max Analogue 5V voltage: 5 VDC +/- 5% Analogue 5V current: 0.15 Amps max	None	

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/ Significant Deviations	Results
			Serial Communication Protocols: RS485 connection to Interface board RS232 connection to blood gas analyzer Digital I/O: Peltier control Reset Analogue interfaces: Pressure sensor amplifiers x 2 Thermistor amplifiers x 3 Glucose dial x 1		
DC – DC Board requirements	1 Device	Internal Method	Input supply voltage 24 VDC +/-20% Peltier output voltage when not current limited 24 VDC max Peltier maximum output current 15 Amps Blood gas analyzer supply voltage 12 VDC +/- 5% Blood gas analyzer supply current 3 Amps max	None	

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/ Significant Deviations	Results
			12 Volt ancillary power supply voltage 12 VDC +/- 5% 12 Volt ancillary power supply current 8.25 Amps max 24 Volt ancillary power supply voltage 24 VDC +/- 5% 24 Volt ancillary power supply current 6 Amps max 5V Logic supply voltage 5V +/-5% 5V Logic supply current 0.2 Amps max		
Trinamics board requirements	1 Device	Internal Method	Integrate the following 24-Volt motor controllers: TMCM 163 BLDC Controller x 2: Blood pump; and nutrient pump TMCM 113 Stepper motor controller x 3: Portal Pinch Valve; Arterial Pinch Valve; and Bile Pinch Valve Power rails:	None	

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/ Significant Deviations	Results
			24RAW voltage: 24 VDC +/-10% 24RAW current: 10 Amps max 24VRegulated voltage: 24VDC +/- 10% 24VRegulated current: 4 Amps max 3V3SPI voltage: 3.3 VDC +/-5% 3V3SPI current: 0.5amps max Serial communication: SPI to UART(RS232) x 6		
Oxygen concentrator control module requirements	1 Device	Internal Method	Input supply voltage: 24 VDC +/-10% Input supply current: 3 Amps max Concentrator supply voltage: 19VDC +/-10% Serial communication protocols: USB to concentrator (unidirectional) Digital I/O from Interface board: Concentrator enable Oxygen demand PWM Concentrator Alarm	None	

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/ Significant Deviations	Results
			Diverter solenoid power: 24 VDC (pwm driven)		
Product Requirements	81 Devices	Internal Protocol	All requirements are located within internal protocol	None	Pass
Road Transit Testing	1 Device	Internal Protocol	Product requirement specification 1.3, 1.5, 1.6, 1.12, 1.13, 1.20, 1.40, 1.43, 1.44, 1.47, 2.1, 27.1, 27.3	None	Pass
Human Factors	1 Device	ISO 62366:2007 AAMI/ANSI HE75:2009	Establishing a baseline of user performance, establishing and validating user performance measures, and identifying potential design concerns	None	Complies
Durability	1 Device	TRA-043105-27-TP-01B	Environmental Test Procedure in accordance with test plan TRA-043105-27-TP-01B Functional checks of the device under test: For operational testing: The device was operated without an organ and the performance of the hemodynamic controller,	Two errors were noted on the control panel screen during the Test 002 – Z-Axis – Broadband Random Road Transport Vibration Test, however, these were reset and cleared after	Pass

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/ Significant Deviations	Results
			thermal controller was monitored via the GUI and by noting any flow or temperature alarms present on the GUI. In addition, the integrity of the system was monitored for mechanical failure or wear-out and by monitoring system alarms (i.e., battery status alarms, blood pump failure alarm, or pinch valve failure alarms etc.). For non-operational stress testing (environmental conditioning) the device was switched on after each test in accordance with the test plan and placed in perfusion mode, without an organ. Alarms were monitored as above and any worn or damaged components noted. In all cases unexpected	the test and no further issues were reported throughout the remainder of the vibration and shock tests.	

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/ Significant Deviations	Results
			alarms, or alarms that would not self-resolve, component failure, or wear-out would constitute a premature failure of the device during the accelerated life testing.		
Biocompatibility	Component review	ISO 10993-1:2009	All surfaces that are in contact with patients and operators are biocompatible	None	Complies
Cleaning Validation	1 Device	Internal Protocol	To establish a validated cleaning regime	None	Pass
Device reliability	9 Liver Perfusion Circuits/3 Retained Unit	Internal Method	To evaluate the performance of the *metra*® Liver Perfusion Circuit following all expected per-use environmental conditioning and use under stressed conditions, for a period of twice the intended device usage life. Testing to be conducted over 48-hours.	None	Complies
Flow sensor accuracy	2 flow sensors	Internal Method	Flows ≤1.0 L/min ±0.07 L/min Flows >1.0 L/min ±7% of reading	None	Pass

Table 4: OrganOx *metra*® System Testing Summary

Test Performed	Device Description/ Sample Size	Test Method/Applicable Standard	Acceptance Criteria	Unexpected Results/Significant Deviations	Results
Usability Engineering	1 Device	IEC 60601-1-6:2010 ISO 62366:2007	Compliance with IEC 60601-1-6:2010 and ISO 62304	none	Pass
Software Static Analysis	1 Device	ISO 62304:2006 + A1:2015	Compliance with ISO 62304	none	Pass
GUI Software Verification	1 Device	ISO 62304:2006 + A1:2015	Compliance with ISO 62304	none	Pass
Software Integration Testing	1 Device	ISO 62304:2006 + A1:2015	Compliance with ISO 62304	none	Pass
Software system Testing	1 Device	ISO 62304:2006 + A1:2015	Compliance with ISO 62304	none	Pass
Wireless monitoring Verification	1 Device	ISO 62304:2006 + A1:2015	Compliance with ISO 62304	none	Pass
Durability Testing	1 Device	TRA-043105-27-TP-01B	Environmental Test Procedure in accordance with test plan TRA-043105-27-TP-01B Functional checks of the device under test: For operational testing: The device was operated without an organ and the performance of the hemodynamic	Two errors were noted on the control panel screen during the Test 002 – Z-Axis – Broadband Random Road Transport Vibration Test, however these were reset and cleared after the test and no further issues were reported throughout the remainder of the vibration and shock tests.	Pass

			controller, thermal controller was monitored via the GUI and by noting any flow or temperature alarms present on the GUI. In addition, the integrity of the system was monitored for mechanical failure or wear-out and by monitoring system alarms (i.e., battery status alarms, blood pump failure alarm, or pinch valve failure alarms etc.). For non-operational stress testing (environmental conditioning) the device was switched on after each test in accordance with the test plan and placed in perfusion mode, without an organ. Alarms were monitored as above and any worn or damaged components noted. In all cases unexpected alarms, or alarms that		

			would not self-resolve, component failure, or wear-out would constitute a premature failure of the device during the accelerated life testing.		

D. Animal Studies

Early animal studies were conducted at the Nuffield Department of Medical Sciences, Oxford University. Due to the nature of this early scientific work, there are no final protocols and reports signed by the study director for each of the animal studies.

These early animal studies were used as safety data to identify risk associated with the design of the clinical trials device, to influence future designs, to design pivotal trials and to be used in the feasibility stage of device development. Although the animal studies informed the non-clinical and clinical studies presented in support of this PMA, the Agency did not directly consider this information in its decision on this PMA.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a US clinical study to establish a reasonable assurance of safety and effectiveness of the OrganOx *metra*® System for use in donor livers destined for transplantation in a functioning state for periods of up to 12 hours under IDE G140243. This data was supported with additional data from a European clinical study, COPE WP02. Data from these clinical studies (**Table 5**) were the bases for the PMA approval decision. A summary of the clinical studies is presented below.

Table 5: Supporting Clinical Studies

Study	OrganOx *metra*® (NMP) liver recipients	Static Cold Storage (SCS) liver recipients
US IDE Study (WP01; G140243)	n = 136	n = 130
European Consortium for Organ Preservation in Europe (COPE) WP02 Study	n = 121	n = 101

A summary of the US WP01 clinical study is presented below. A summary of the COPE WP02 study is presented in Section XI ("Summary of Supplemental Clinical Information") of this SSED document.

US Study WP01 (IDE G140243)

A. Study Design

Patients were enrolled between October 9, 2016, and February 3, 2020. The data for this PMA was collected through the final database lock on July 1, 2021, and included 267 enrolled subjects, 266 transplanted livers (136 in the NMP arm and 130 in the SCS arm), and 383 randomized livers. There were 15 investigational sites, 14 of which enrolled patients.

Data from the pivotal WP01 Study (via IDE G140243) was used to support the safety and effectiveness of the OrganOx *metra*®. The WP01 study was a multicenter, open label, randomized (1:1), controlled, non-blinded clinical trial comparing the efficacy of *ex-vivo* normothermic machine perfusion (NMP) using the OrganOx *metra*® device with static cold storage (SCS) in human liver transplantation. Subjects enrolled in the study were followed for 12 months (Days 1-7, Day 10, Day 30, Month 3, Month 6, and Month 12) post-transplant procedure.

Donor livers were randomly assigned to the NMP or SCS arm with a 1:1 allocation as per a computer-generated randomization schedule using variable block randomization and the following stratification factors: participating (recipient) center and donor type (donation after brain death; DBD or donation after circulatory death; DCD). The randomization schedule was created by the study statistician and the size of the randomization blocks were known only to the study statistician and the Data Safety Monitoring Board (DSMB) statistician. A core laboratory was utilized to perform pathology evaluations of the study liver biopsies. The core lab histopathologists were blinded to randomization assignment, primary endpoints, and primary and secondary outcome results by randomization group. OrganOx representatives were blinded to primary endpoints and secondary outcome results by randomization group. Local investigators were blinded to primary and secondary outcome results by randomization group.

All adverse events collected through follow-up were reviewed by an independent Medical Monitor. A Clinical Events Committee (CEC) adjudicated the most critical adverse events, and a DSMB reviewed aggregate safety data.

1. Clinical Inclusion and Exclusion Criteria

   Randomization in the WP01 clinical study was limited to donor livers that met the following inclusion criteria:

   Donor Inclusion Criteria

   1. Donation after brain death (DBD) donor aged 40 years or greater
   2. Donation after circulatory death (DCD) donor aged 16 years or greater
   3. Liver allograft from DBD or DCD donors

Randomization of livers was not permitted in the WP01 clinical study if they met any of the following exclusion criteria:

Donor Exclusion Criteria

1. Living donor liver
2. Liver intended for split transplant
3. Liver which Investigator is unwilling to randomize to either arm

Enrollment in the WP01 clinical study was limited to subjects (recipients) that met the following inclusion criteria:

Recipient Inclusion Criteria

1. Subject is 18 years of age or greater

2. Subject is registered as an active recipient on the UNOS waiting list for liver transplantation

3. Subject, or legally authorized representative, is able and willing to give informed consent and HIPAA authorization

4. Subject is able and willing to comply with all study requirements (in the opinion of the Investigator)

Subjects were not permitted to enroll in the WP01 clinical study if they met any of the following exclusion criteria:

Recipient Exclusion Criteria

1. Subject requiring all the following at the time of transplantation:
    a. Oxygen therapy via a ventilator/respirator
    b. Inotropic support
    c. Renal replacement therapy

2. Subject has acute/fulminant liver failure (UNOS status 1A)

3. Subject undergoing simultaneous transplantation of more than one organ (e.g., liver and kidney)

4. Subject is pregnant (as confirmed by urine or serum pregnancy test) or nursing

5. Concurrent enrollment in another clinical trial. Subjects enrolled in clinical trials or registries where only measurements and/or samples are taken (no test device or test drug used) are allowed to participate.

2. Follow-up Schedule

All transplanted subjects were assessed daily (Days 1-7) and on Day 10 by their clinical team and managed according to standard local protocols during their post-transplant inpatient stay.

Subjects were scheduled to return for follow-up examinations at the following post-transplant timepoints:

- Day 30 (± 7 days)
- Month 3 (± 14 days)
- Month 6 (± 14 days)
- Month 12 (± 30 days)

Preoperative information on donor and recipient demographics was collected along with the EQ-5D quality of life questionnaire. Postoperatively, the objective parameters measured during the study included biochemical assessments in addition to assessments for primary non-function (PNF), graft survival, subject survival, resource use, safety outcomes, readmissions, and renal replacement therapy requirement. The EQ-5D quality of life questionnaire was also completed at the Month 6 follow-up. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

Primary Endpoint

The pre-specified primary endpoint was to compare the effect of NMP to SCS in preventing preservation-related graft injury as measured by early allograft dysfunction (EAD) during Days 1-7. EAD was defined as the presence of one of the following three outcomes:

1. Serum bilirubin ≥ 10 mg/dL at Day 7 post-transplant
2. International normalized ratio ≥ 1.6 at Day 7 post-transplant
3. Alanine aminotransferase ALT or aspartate aminotransferase AST > 2000 IU/L within the first 7 days post-transplant

The primary endpoint analysis was performed on all transplanted subjects. The hypothesis was written as follows:

$$H_0: EAD_{NMP} \geq EAD_{SCS}$$
$$H_A: EAD_{NMP} < EAD_{SCS}$$

A one-sided significance level of $\alpha = 0.025$ was used to test the primary endpoint; therefore, if the hypothesis test results in a one-sided p-value that is less than 0.025, the study would be considered a success.

Secondary Endpoints

The pre-specified secondary endpoints are listed below and compared between NMP and SCS arms:

- To compare graft and subject survival between NMP and SCS livers based on PNF rates during the first 10 days after liver transplant; graft survival rates at 30 days, 3 months, and 6 months after liver transplant; and subject survival rates at 30 days, 3 months, and 6 months after liver transplant

- To compare evidence of post-reperfusion syndrome between NMP and SCS livers on transplantation based on mean arterial pressure pre- and post-reperfusion in the context of vasopressor use

- To compare biochemical liver function between NMP and SCS livers based on bilirubin, gamma glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and international normalized ratio (INR) at Days 1-7, Day 30, Month 3, and Month 6 post-transplant. Additionally, lactate measurements were taken at Days 1-7 while the subject was in the ICU

- To compare evidence of ischemia-reperfusion injury between NMP and SCS livers based on post-reperfusion biopsies compared to baseline pre-reperfusion biopsies and graded according to standard histological criteria

- To compare evidence of biliary complications between NMP and SCS livers based on incidence of biliary investigations and/or interventions between 7 days and 6 months post-transplant. Biliary investigations include magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, and percutaneous transhepatic cholangiography. Biliary interventions include those that are surgical, radiological, or endoscopic in nature

- To assess the feasibility and safety of NMP as a method of organ storage and transportation based on incidences of one or more of the following per randomized liver: (i) EAD; (ii) discard (non-transplant) of a retrieved liver; (iii) primary non-function

- To compare organ utilization between NMP and SCS livers based on incidence of livers randomized but not transplanted and reasons for not transplanting

- To assess the health economic implications of normothermic liver perfusion based on logistical and healthcare costs and quality of life measures

No formal hypothesis testing was performed on the secondary endpoints

B. Accountability of PMA Cohort

Fifteen investigative sites were initiated during the study, fourteen of which enrolled study subjects. One site screened subjects throughout the study but did not enroll any subjects.

As detailed in **Figure 3**, a total of 383 livers were randomized into either the NMP group (n=192) or SCS group (n=191). There were 267 enrolled subjects with 266 transplanted livers (136 in the NMP arm and 130 in the SCS arm). One liver was allocated to a study subject who was found to be inoperable at the start of surgery; the donor liver was reallocated to a second consented subject.

At the time of the database lock, of the 267 subjects enrolled in the IDE study, 91.0% (243/267) of the subjects were available for analysis at the completion of the Month 12 post-transplant visit. The dataset included data for all eligible subjects through the Month 12 follow-up visit. 99.6% of subjects that were not exited from the study before Month 12 completed their Month 12 follow-up visit. Of enrolled subjects, 89.7% (122/136) of the NMP subjects and 92.4% (121/131) of the SCS subjects completed the Month 12 follow-up visit. The remaining Month 12 visits in each arm were not completed, as the subjects were exited from the study prior to the Month 12 follow-up visit.

One enrolling site elected to discontinue participation during the study after enrolling two subjects and was closed following completion of subject follow-up at Month 12.

Table 6 provides the detailed breakdown of subject disposition by randomization group and donor type along with the reason for study exit of livers that did not proceed to transplant. The flowchart in **Figure 3** contains the data analysis for the final ITT population.

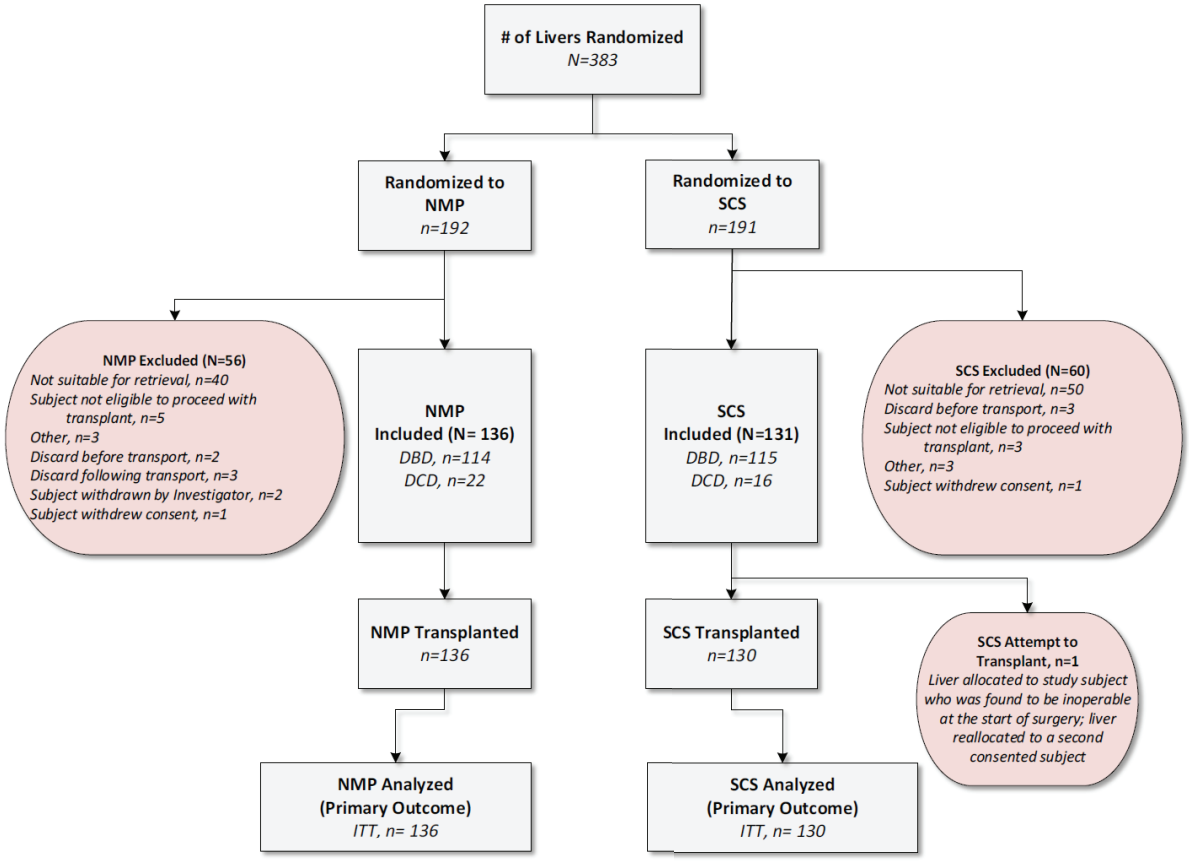

Figure 3 – Study Accountability Flowchart

A total of 116 randomized livers were excluded from the study (56 NMP, 60 SCS). Of these livers, 90 livers were deemed unsuitable for retrieval for transplant by the study investigators (40 NMP, 50 SCS). Of these 90 livers, 86 livers were not procured (38 NMP, 48 SCS). Further information about the 90 livers deemed unsuitable are provided below:

- Forty-six livers where the donor did not proceed (DCD donor did not proceed to donation or prolonged warm ischemic time, outside of local criteria for liver transplantation) (20 NMP, 26 SCS)
- Twenty-one livers due to donor liver quality (cirrhosis/fibrosis/steatosis) (9 NMP, 12 SCS)
- Fourteen livers due to other reasons (5 NMP, 9 SCS)
- Two livers due to injury to the hepatic artery (1 NMP, 1 SCS)
- One liver due to injury to the IVC/parenchymal damage (1 NMP, 0 SCS)
- One liver due to abnormal lesion within the liver (1 NMP, 0 SCS)
- One liver due to donor problem (1 NMP, 0 SCS)
- Two livers were procured for research purposes (1 NMP, 1 SCS)
- Two livers were procured and transplanted outside of the study (1 NMP, 1 SCS)

Of the remaining twenty-six livers that were excluded from the study:

- Eight livers were excluded because the subject was not medically suitable (eligible) on the day to proceed with the transplant (5 NMP, 3 SCS)
- Five livers were discarded following retrieval, prior to transport (2 NMP, 3 SCS)
- Three livers were discarded following transport (3 NMP, 0 SCS)
- Two livers were excluded because the subject was withdrawn by the investigator (2 NMP, 0 SCS) due to cardiac issues (1 NMP) and heart arrhythmia (1 NMP)
- Two livers were excluded because the subject withdrew consent (1 NMP, 1 SCS)
- Six livers were excluded for other reasons (3 NMP, 3 SCS)

Table 6: Subject Disposition by Randomized Group and Donor Type

	Overall		DBD		DCD	
	NMP	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Randomized	192	191	143	144	49	47
Enrolled (knife-to-skin contact)	136	131	114	115	22	16
If enrolled, donor type						
DBD	114	115	114	115	0	0
DCD	22	16	0	0	22	16
Not Enrolled (no knife-to-skin contact)	56	60	29	29	27	31
Reason for study exit						
Liver not Suitable for Retrieval	40	50	15	22	25	28
Liver Discarded Before Transport	2	3	1	2	1	1
Liver Discarded Following Transport	3	0	3	0	0	0
Subject was not Eligible to Proceed withTransplant	5	3	4	3	1	0
Subject Withdrew Consent	1	1	1	0	0	1
Subject Withdrawn by Investigator	2	0	2	0	0	0
Other	3	3	3	2	0	1
Transplanted	136	130	114	114	22	16

If transplanted, Per-Protocol analysis group						
NMP*	133	0	113	0	20	0
SCS	0	130	0	114	0	16
If transplanted, As-Treated analysis group						
NMP*	133	2	113	1	20	1
SCS	0	130	0	114	0	16
Re-allocated	0	1	0	1	0	0
*One subject (AGBX122) was excluded from the analysis due to exclusion criteria being met. Two additional subjects (AEJX212, AELD404) were excluded due to being transported using Static Cold Storage.						

The primary analysis was performed on all subjects in the intent-to-treat (ITT) population. Per the protocol and statistical analysis plan, additional sensitivity analyses included:

- Analysis of donor type crossovers per the corrected donor type
- Analysis of preservation type where any livers randomized to the NMP arm, but unable to be preserved on the machine and therefore preserved using SCS, were analyzed in the SCS arm
- Multiple imputation for EAD status that is unable to be confirmed by complete labs or at least 1 lab value meeting criteria for EAD
- Per Protocol analysis: For item 1 in the list above, there were no transplanted livers where the donor type was corrected and considered a crossover, therefore no results are presented

The following is a summary of the populations analyzed:

- The ITT population includes all transplanted subjects (a subject with reperfusion of a donor liver) and analyzes them in the groups to which the liver was randomly assigned, irrespective of whether the assigned method of preservation was actually used
- The Per-Protocol population includes all transplanted subjects who were followed according to the protocol procedures with no major deviations:

- One subject (Subject 08-021/Liver AGBX122) was excluded from the Per-Protocol analysis due to exclusion criteria being met

- Two subjects (Subject 13-003/Liver AEJX212 and Subject 06-019/Liver AELD404) were excluded from the Per-Protocol analysis as they were randomized to NMP but were unable to be placed on the device and instead were transported using SCS

- The As-Treated population includes all transplanted subjects and analyzes them in the treatment groups corresponding to the method of preservation that was actually used.

  - One subject (Subject 08-021/Liver AGBX122) was excluded from the As-Treated analysis due to exclusion criteria being met

  - Two subjects (Subject 13-003/Liver AEJX212 and Subject 06-019/Liver AELD404) were included in the SCS arm in the As-Treated analysis because they received livers that were randomized to NMP but were unable to be placed on the device and instead were transported using SCS

There were three subjects (Subject 08-017/Liver AFJX183, Subject 03-049/Liver AGJY324, and Subject 09-002/Liver AECG396) identified as having elevated Day 7 INR values due to therapeutic anticoagulation. Day 7 INR values for these three subjects were therefore considered missing for all analyses and imputed to determine EAD status.

C. Study Population Demographics and Baseline Parameters

Table 7 summarizes the baseline demographics of the donors in the intent-to-treat (ITT) cohort. The demographics of the study population are typical for a liver transplant study.

Table 7: Donor Demographics with Attempted Transplant

	Overall		DBD		DCD	
Characteristic	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Age (years)						
N	136	130	114	114	22	16
Mean ± SD	53.1 ± 12.9	52.5 ± 11.5	56.5 ± 9.3	54.4 ± 9.7	35.6 ± 15.2	38.7 ± 14.4
Median	54.0	52.0	56.0	53.0	30.5	37.0
Range (Min, Max)	(18.0, 80.0)	(20.0, 79.0)	(40.0, 80.0)	(40.0, 79.0)	(18.0, 66.0)	(20.0, 61.0)
IQR	47.0, 60.0	45.0, 60.0	49.0, 62.0	47.0, 61.0	22.0, 47.0	27.0, 50.0
Sex						
Male	45.6% (62/136)	52.3% (68/130)	43.0% (49/114)	50.9% (58/114)	59.1% (13/22)	62.5% (10/16)

	Overall		DBD		DCD	
Characteristic	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Female	54.4% (74/136)	47.7% (62/130)	57.0% (65/114)	49.1% (56/114)	40.9% (9/22)	37.5% (6/16)
Race						
American Indian or Alaskan Native	0.7% (1/136)	0.8% (1/130)	0.0% (0/114)	0.9% (1/114)	4.5% (1/22)	0.0% (0/16)
Asian	0.0% (0/136)	0.8% (1/130)	0.0% (0/114)	0.9% (1/114)	0.0% (0/22)	0.0% (0/16)
Black or African American	18.4% (25/136)	20.8% (27/130)	21.1% (24/114)	23.7% (27/114)	4.5% (1/22)	0.0% (0/16)
Native Hawaiian or other Pacific Islander	0.0% (0/136)	0.0% (0/130)	0.0% (0/114)	0.0% (0/114)	0.0% (0/22)	0.0% (0/16)
White	77.9% (106/136)	75.4% (98/130)	76.3% (87/114)	73.7% (84/114)	86.4% (19/22)	87.5% (14/16)
Other	2.9% (4/136)	2.3% (3/130)	2.6% (3/114)	0.9% (1/114)	4.5% (1/22)	12.5% (2/16)
Ethnicity						
Hispanic or Latino	23.1% (9/39)	25.0% (10/40)	24.2% (8/33)	21.6% (8/37)	16.7% (1/6)	66.7% (2/3)
Not Hispanic or Latino	76.9% (30/39)	75.0% (30/40)	75.8% (25/33)	78.4% (29/37)	83.3% (5/6)	33.3% (1/3)
Selected Medical History						
Diabetes	18.0% (24/133)	11.8% (15/127)	20.7% (23/111)	13.5% (15/111)	4.5% (1/22)	0.0% (0/16)
Smoker	52.7% (69/131)	47.2% (60/127)	53.2% (58/109)	45.9% (51/111)	50.0% (11/22)	56.3% (9/16)
History of Heavy Alcohol Use	19.5% (26/133)	22.8% (29/127)	21.4% (24/112)	23.4% (26/111)	9.5% (2/21)	18.8% (3/16)
History of Illicit Drug Use	35.1% (47/134)	41.3% (52/126)	33.0% (37/112)	40.5% (45/111)	45.5% (10/22)	46.7% (7/15)
Diagnosis of Hepatitis C Virus (HCV)	8.1% (11/136)	3.8% (5/130)	8.8% (10/114)	3.5% (4/114)	4.5% (1/22)	6.3% (1/16)
Diagnosis of Hepatocellular Carcinoma (HCC)	0.0% (0/136)	0.0% (0/130)	0.0% (0/114)	0.0% (0/114)	0.0% (0/22)	0.0% (0/16)
Body Mass Index (BMI) (kg/m^2)						

	Overall		DBD		DCD	
Characteristic	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
N	136	130	114	114	22	16
Mean ± SD	30.2 ± 7.9	29.4 ± 6.9	30.5 ± 8.4	29.8 ± 6.9	28.9 ± 5.1	26.6 ± 6.3
Median	29.2	28.3	29.2	28.5	29.3	25.3
Range (Min, Max)	(18.2, 80.7)	(17.3, 51.0)	(18.2, 80.7)	(17.8, 51.0)	(20.7, 37.8)	(17.3, 44.9)
IQR	25.6, 33.8	24.5, 32.6	25.6, 34.6	25.1, 33.1	25.9, 32.6	23.0, 28.0
Denominator includes all donors that have a demographics assessment date Data reported as 'unknown' are considered as missing						

Table 8 summarizes baseline characteristics of the donors with attempted transplants. There were no major differences in cause of death or mean donor risk index (DRI) between the randomization arms.

Table 8: Donor Baseline Characteristics with Attempted Transplant

	Overall		DBD		DCD	
Characteristic	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Cause of Death						
Cerebrovascular Accident (CVA)	37.5% (51/136)	44.6% (58/130)	40.4% (46/114)	47.4% (54/114)	22.7% (5/22)	25.0% (4/16)
Hypoxia	2.2% (3/136)	1.5% (2/130)	0.9% (1/114)	1.8% (2/114)	9.1% (2/22)	0.0% (0/16)
Trauma	15.4% (21/136)	15.4% (20/130)	14.0% (16/114)	13.2% (15/114)	22.7% (5/22)	31.3% (5/16)
Anoxia	40.4% (55/136)	34.6% (45/130)	41.2% (47/114)	35.1% (40/114)	36.4% (8/22)	31.3% (5/16)
Other	4.4% (6/136)	3.8% (5/130)	3.5% (4/114)	2.6% (3/114)	9.1% (2/22)	12.5% (2/16)
Donor Risk Index (DRI)						
N	136	130	114	114	22	16
Mean ± SD	1.6 ± 0.3	1.6 ± 0.3	1.6 ± 0.3	1.6 ± 0.3	1.9 ± 0.4	1.9 ± 0.5
Median	1.6	1.6	1.5	1.6	1.9	1.7
Range (Min, Max)	(1.1, 2.8)	(1.0, 3.1)	(1.1, 2.4)	(1.0, 2.3)	(1.4, 2.8)	(1.4, 3.1)
IQR	1.4, 1.8	1.4, 1.8	1.3, 1.8	1.4, 1.8	1.5, 2.1	1.6, 2.0

Donor livers randomized into the NMP and SCS arms were generally comparable with respect to donor baseline characteristics and demographics. Additionally, the proportion of male and female donors was comparable across arms.

DBD donors were middle aged (44 to 67 years old) and had a low donor risk index (DRI; 1.6). DCD donors were younger (20 to 45 years old) and had a high DRI (1.9). All the above characteristics were comparable across arms.

Table 9 summarizes the baseline demographics of the 267 enrolled subjects (136 NMP, 131 SCS).

Table 9: Recipient Demographics by Donor Type and Randomization Arm

	Overall		DBD		DCD	
Characteristic	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Age (years)						
N	136	131	114	115	22	16
Mean ± SD	57.4 ± 10.5	57.2 ± 10.6	57.7 ± 10.4	57.8 ± 10.5	55.8 ± 11.3	52.6 ± 10.3
Median	59.0	60.0	59.5	60.0	58.0	55.0
Range (Min, Max)	(20.0, 76.0)	(21.0, 77.0)	(21.0, 76.0)	(21.0, 77.0)	(20.0, 73.0)	(37.0, 67.0)
IQR	54.0, 64.0	52.0, 65.0	54.0, 64.0	53.0, 65.0	53.0, 62.0	42.0, 59.0
Sex						
Male	68.4% (93/136)	63.4% (83/131)	69.3% (79/114)	66.1% (76/115)	63.6% (14/22)	43.8% (7/16)
Female	31.6% (43/136)	36.6% (48/131)	30.7% (35/114)	33.9% (39/115)	36.4% (8/22)	56.3% (9/16)
Race						
American Indian or Alaskan Native	0.0% (0/136)	0.0% (0/131)	0.0% (0/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
Asian	0.0% (0/136)	0.8% (1/131)	0.0% (0/114)	0.9% (1/115)	0.0% (0/22)	0.0% (0/16)
Black or African American	3.7% (5/136)	6.9% (9/131)	3.5% (4/114)	7.0% (8/115)	4.5% (1/22)	6.3% (1/16)
Native Hawaiian or other Pacific Islander	0.0% (0/136)	0.0% (0/131)	0.0% (0/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
White	93.4% (127/136)	90.8% (119/131)	93.0% (106/114)	90.4% (104/115)	95.5% (21/22)	93.8% (15/16)
Other	2.9% (4/136)	0.8% (1/131)	3.5% (4/114)	0.9% (1/115)	0.0% (0/22)	0.0% (0/16)
Ethnicity						
Hispanic or Latino	11.0% (15/136)	9.9% (13/131)	11.4% (13/114)	9.6% (11/115)	9.1% (2/22)	12.5% (2/16)

	Overall		DBD		DCD	
Characteristic	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Not Hispanic or Latino	89.0% (121/136)	90.1% (118/131)	88.6% (101/114)	90.4% (104/115)	90.9% (20/22)	87.5% (14/16)
Etiology of Liver Disease/ Indication for Liver Transplant*						
Hepatocellular Disease	81.6% (111/136)	85.5% (112/131)	83.3% (95/114)	87.8% (101/115)	72.7% (16/22)	68.8% (11/16)
Cholestatic Liver Disease	8.1% (11/136)	6.9% (9/131)	6.1% (7/114)	7.0% (8/115)	18.2% (4/22)	6.3% (1/16)
Vascular Disease	0.7% (1/136)	0.0% (0/131)	0.9% (1/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
Metabolic disorder and metabolic liver disease	5.1% (7/136)	6.1% (8/131)	5.3% (6/114)	5.2% (6/115)	4.5% (1/22)	12.5% (2/16)
Primary Hepatocellular carcinoma	31.6% (43/136)	29.8% (39/131)	35.1% (40/114)	29.6% (34/115)	13.6% (3/22)	31.3% (5/16)
Toxic reactions	0.0% (0/136)	1.5% (2/131)	0.0% (0/114)	0.9% (1/115)	0.0% (0/22)	6.3% (1/16)
Trauma	0.0% (0/136)	0.0% (0/131)	0.0% (0/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
Other	11.0% (15/136)	12.2% (16/131)	8.8% (10/114)	10.4% (12/115)	22.7% (5/22)	25.0% (4/16)
Body Mass Index (BMI) (kg/m^2)						
N	136	131	114	115	22	16
Mean ± SD	29.2 ± 5.7	29.5 ± 6.0	29.4 ± 5.8	29.8 ± 5.8	27.8 ± 4.9	27.7 ± 7.5
Median	28.3	28.9	28.7	29.1	26.6	26.4
Range (Min, Max)	(18.5, 49.3)	(16.8, 49.5)	(18.5, 49.3)	(16.8, 49.5)	(21.8, 41.4)	(18.7, 47.4)
IQR	25.4, 32.0	25.4, 33.0	25.6, 32.1	25.6, 33.2	24.9, 30.3	22.1, 31.5
Selected Medical History						
Smoker	31.9% (43/135)	26.2% (34/130)	32.7% (37/113)	25.4% (29/114)	27.3% (6/22)	31.3% (5/16)
History of Heavy Alcohol Use	37.1% (49/132)	33.1% (43/130)	38.7% (43/111)	31.6% (36/114)	28.6% (6/21)	43.8% (7/16)
Re-transplant	0.7% (1/136)	1.5% (2/131)	0.9% (1/114)	1.7% (2/115)	0.0% (0/22)	0.0% (0/16)
If re-transplant, cause of failure of previous liver transplant*						
Primary graft non-function	0.0% (0/136)	0.0% (0/131)	0.0% (0/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
Hepatic artery thrombosis	0.0% (0/136)	0.0% (0/131)	0.0% (0/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
Chronic rejection	0.0% (0/136)	1.5% (2/131)	0.0% (0/114)	1.7% (2/115)	0.0% (0/22)	0.0% (0/16)

	Overall		DBD		DCD	
Characteristic	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Ischemic type biliary lesions after donation after cardiac death	0.0% (0/136)	0.0% (0/131)	0.0% (0/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
Recurrent non-neoplastic disease causing late graft failure	0.0% (0/136)	0.0% (0/131)	0.0% (0/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
Recurrence of original liver disease	0.7% (1/136)	0.0% (0/131)	0.9% (1/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
Other	0.0% (0/136)	0.8% (1/131)	0.0% (0/114)	0.9% (1/115)	0.0% (0/22)	0.0% (0/16)

*Multiple responses are possible for 1 subject
† Denominator includes all subjects that have a demographics assessment date
Data reported as 'unknown' are considered as missing

In the US WP01 study, the 136 NMP recipients comprised of 93 males (68.4%) and 43 females (31.6%) with a mean age of 57.4 ± 10.5 years. The 131 recipients in the SCS group comprised of 83 males (63.4%) and 48 females (36.6%) with a mean age of 57.1 ± 10.6 years.

There were no notable differences in the age of recipients and percentage of males between the NMP and SCS groups. A high proportion of recipients overall were white males.

The mean calculated MELD score for the NMP arm (N = 134) was 19.2±9.5 and 19.4±8.8 for the SCS arm (N = 130). MELD scores in the NMP-DBD (N = 112) subgroup were 19.6±9.9 and 19.3±9.3 in the SCS-DBD subgroup (N = 114). MELD scores in the NMP-DCD subgroup (N = 22) were 17.3±7.0 and 20.3±4.7 in the SCS-DCD subgroup (N = 16). There were no notable differences in the mean calculated MELD scores across arms.

The site-reported MELD score for the NMP arm was 26.5±6.5 and 26.6±6.2 for the SCS arm. Site-reported MELD scores in the NMP-DBD subgroup were 27.0±6.5 and 27.0±6.2 in the SCS-DBD subgroup. Site-reported MELD scores in the NMP-DCD subgroup were 23.9±6.2 and 24.4±5.4 in the SCS-DCD subgroup. Sample sizes for each arm and subgroup are the same as those mentioned in the paragraph above. There were no notable differences in the mean site-reported MELD scores across arms.

The highest proportion of MELD scores were in the 15-30 category for both randomization arms in the calculated and site-reproted scores. The expected survival benefit is greatest for subjects with high MELD scores and minimal for subjects with low MELD scores (< 15).

Table 10 summarizes preservation times for NMP and SCS livers. The mean total preservation time using the As-Treated population was 75% longer in the NMP arm of the study compared to the SCS arm (NMP 553.8 ± 115.9 minutes; SCS 316.9 ± 94.1 minutes).

Table 10: NMP and SCS Preservation Times (As-Treated Analysis)

	Overall		DBD		DCD	
Measure	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Cold Ischemia Time (minutes)[1]						
N	134	132	113	115	21	17
Mean ± SD	134.9 ± 35.7	316.9 ± 94.1	130.3 ± 35.2	315.3 ± 95.8	159.9 ± 27.8	328.0 ± 82.8
Median	133.5	303.0	126.0	303.0	156.0	315.0
Range (Min, Max)	(24.0, 229.0)	(143.0, 623.0)	(24.0, 229.0)	(143.0, 623.0)	(122.0, 228.0)	(211.0, 505.0)
IQR	111.0, 157.0	246.0, 370.5	108.0, 153.0	243.0, 368.0	141.0, 172.0	269.0, 395.0
Time on Pump (minutes) - NMP[2]						
N	133	-	112	-	21	-
Mean ± SD	356.2 ± 105.9		349.9 ± 103.7		389.8 ± 113.6	
Median	323.0		322.0		363.0	
Range (Min, Max)	(196.0, 701.0)		(196.0, 701.0)		(256.0, 616.0)	
IQR	269.0, 421.0		262.5, 403.0		297.0, 482.0	
Total Preservation Time (minutes)[3]						
N	134	132	113	115	21	17
Mean ± SD	553.8 ± 115.9	316.9 ± 94.1	543.0 ± 110.0	315.3 ± 95.8	611.5 ± 132.2	328.0 ± 82.8
Median	523.0	303.0	517.0	303.0	577.0	315.0
Range (Min, Max)	(365.0, 890.0)	(143.0, 623.0)	(365.0, 890.0)	(143.0, 623.0)	(439.0, 872.0)	(211.0, 505.0)
IQR	466.0, 617.0	246.0, 370.5	463.0, 594.0	243.0, 368.0	522.0, 676.0	269.0, 395.0

	Overall		DBD		DCD	
Measure	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Functional Warm Ischemia Time (minutes)[4]						
N	20	17	-	-	20	17
Mean ± SD	12.3 ± 4.9	11.4 ± 3.6			12.3 ± 4.9	11.4 ± 3.6
Median	12.5	11.0			12.5	11.0
Range (Min, Max)	(3.0, 22.0)	(7.0, 19.0)			(3.0, 22.0)	(7.0, 19.0)
IQR	9.5, 14.5	9.0, 14.0			9.5, 14.5	9.0, 14.0

[1]Cold ischemia time (NMP) is calculated as time from aortic cold perfusion to initiation of NMP for the DCD arm and time of cross clamp to initiation of NMP for the DBD arm.
[1]Cold ischemia time (SCS) is calculated as time from aortic cold perfusion to portal reperfusion for the DCD arm and time from cross clamp to portal reperfusion for the DBD arm.
[2]Time on pump (NMP) is calculated as time from initiation of NMP to cessation of NMP.
[3]Total preservation time is calculated as time from cross clamp to portal reperfusion in the DBD arm and time from aortic cold perfusion to portal reperfusion in the DCD arm.
[4]Functional warm ischemia time (minutes) is calculated for DCD donors only as onset time of systolic blood pressure falling below 50mmHg (SBP < 50 mmHg) to earlier of time of start of aortic cold perfusion or time of start of portal cold perfusion.

Mean total preservation time (TPT) was longer in the NMP group (9.2 hours) compared to SCS (5.2 hours). The max TPT was 15 hours in the NMP, as compared to 10 hours in the SCS.

The mean cold ischemia time (CIT) in the NMP group was 135.25 ± 35.84 minutes, with no difference in CIT between patients with EAD and those without EAD.

The mean time on NMP was 358.71 ± 107.62 minutes; no significant difference was observed between patients with EAD and those without EAD.

The mean CIT in the SCS group was 319.31 ± 93.76 minutes in recipients who displayed EAD. This is considered an acceptable CIT in SCS livers.

Total operative time was prolonged in the DCD donors (6.3 hours) compared to NMP (5.4 hours). On the contrary, anastomosis time (defined as the time between removal of organ from ice (SCS) or perfusion device (NMP) to organ reperfusion) was prolonged in the NMP (50 to 55 minutes) compared to the SCS group (33 minutes).

Table 11 shows procedural details for the NMP and SCS groups. The mean total operative time was similar between the groups (NMP 350.2 minutes; SCS 345.5 minutes). The increased mean anastomotic time reported for NMP livers (NMP 60.2 ± 22.3 versus SCS 38.5 ± 19.2) was not due to an increase in operative time. The increased

time was due to inclusion of the cold flush time following cessation of NMP in the calculation of anastomotic time, which is not required for SCS livers.

Of note is the reduction in the occurrence of post-reperfusion syndrome in the NMP arm of the study (NMP 5.9%; SCS 14.6%).

Table 11: Summary of Liver Procedures

	Overall		DBD		DCD	
Characteristic	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Total Operative Time (mins.)						
N	136	131	114	115	22	16
Mean ± SD	350.2 ± 110.1	345.5 ± 112.5	345.1 ± 107.9	342.8 ± 107.4	376.6 ± 119.8	365.3 ± 146.6
Median	332.5	326.0	328.0	324.0	381.5	381.0
Range (Min, Max)	(133.0, 670.0)	(104.0, 788.0)	(133.0, 670.0)	(104.0, 651.0)	(175.0, 588.0)	(160.0, 788.0)
IQR	277.0, 405.5	267.0, 409.0	277.0, 401.0	267.0, 408.0	281.0, 481.0	262.0, 429.0
Anastomotic time (secondary warm ischemia)[1] (mins.)						
N	132	129	110	113	22	16
Mean ± SD	60.2 ± 22.3	38.5 ± 19.2	60.1 ± 22.7	38.7 ± 19.5	60.2 ± 20.5	37.4 ± 17.2
Median	57.0	33.0	57.0	33.0	55.5	33.5
Range (Min, Max)	(22.0, 138.0)	(5.0, 129.0)	(22.0, 138.0)	(5.0, 129.0)	(28.0, 100.0)	(10.0, 64.0)
IQR	43.0, 73.0	26.0, 46.0	42.0, 72.0	26.0, 43.0	47.0, 75.0	24.0, 50.0
Occurrence of post-reperfusion syndrome [2]	5.9% (8/136)	14.6% (19/130)	4.4% (5/114)	14.0% (16/114)	13.6% (3/22)	18.8% (3/16)
Use of vasopressors prior to and after reperfusion	97.4% (114/117)	99.1% (108/109)	96.9% (95/98)	98.9% (93/94)	100.0% (19/19)	100.0% (15/15)
Intraoperative transfusion of blood and blood products	79.4% (108/136)	84.6% (110/130)	78.1% (89/114)	83.3% (95/114)	86.4% (19/22)	93.8% (15/16)

[1]Defined as time between removal of organ from ice (SCS) or perfusion device (NMP) to organ reperfusion (whichever is first of portal or arterial)
[2]Defined as a decrease in mean arterial pressure (MAP) of more than 30% from the baseline value for more than one minute during the first five minutes after reperfusion

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the ITT cohort of 136 NMP and 131 SCS enrolled patients available for the 12-month evaluation. Adverse events are reported in **Tables 12** to **15.**

Adverse effects that occurred in the US WP01 PMA clinical study:

Table 12 below provides a summary of the serious adverse events (SAEs) that occurred in ≥ 1% of subjects by randomization arm. There were 275 SAEs in 95 subjects in the NMP arm and 244 SAEs in 93 subjects in the SCS arm.

Table 12: SAEs by System and Specific Codes that Occurred in ≥ 1% of Subjects

	NMP n(%)		SCS n(%)	
Safety Event Type	**Patients (N = 136)**	**Events (N = 275)**	**Patients (N = 131)**	**Events (N = 244)**
Hepatic	39 (28.7)	68 (24.7)	37 (28.2)	47 (19.3)
Biliary stricture (anastomotic)	17 (12.5)	20 (7.3)	7 (5.3)	7 (2.9)
Rejection	8 (5.9)	9 (3.3)	16 (12.2)	17 (7.0)
Graft dysfunction	14 (10.3)	14 (5.1)	6 (4.6)	7 (2.9)
Bile leak	3 (2.2)	3 (1.1)	4 (3.1)	4 (1.6)
Cholangitis	5 (3.7)	5 (1.8)	2 (1.5)	2 (0.8)
Other	4 (2.9)	5 (1.8)	3 (2.3)	3 (1.2)
Biliary other	3 (2.2)	3 (1.1)	2 (1.5)	2 (0.8)
Hepatic artery thrombosis	4 (2.9)	4 (1.5)	1 (0.8)	1 (0.4)
Ischemic cholangiopathy	2 (1.5)	2 (0.7)	1 (0.8)	3 (1.2)
Bleeding Complications	15 (11.0)	16 (5.8)	24 (18.3)	26 (10.7)
Bleeding – transfusion required	8 (5.9)	8 (2.9)	12 (9.2)	12 (4.9)
Bleeding requiring reoperation	3 (2.2)	3 (1.1)	11 (8.4)	11 (4.5)
Infection	20 (14.7)	24 (8.7)	17 (13.0)	19 (7.8)
Blood	11 (8.1)	14 (5.1)	6 (4.6)	6 (2.5)
Gastrointestinal	5 (3.7)	5 (1.8)	3 (2.3)	3 (1.2)
Abdominal	2 (1.5)	2 (0.7)	5 (3.8)	5 (2.0)
Other	1 (0.7)	1 (0.4)	3 (2.3)	3 (1.2)
Respiratory	15 (11.0)	16 (5.8)	20 (15.3)	26 (10.7)
Acute Respiratory Failure	6 (4.4)	6 (2.2)	8 (6.1)	8 (3.3)
Other	4 (2.9)	4 (1.5)	7 (5.3)	7 (2.9)

	NMP n(%)		SCS n(%)	
Safety Event Type	**Patients (N = 136)**	**Events (N = 275)**	**Patients (N = 131)**	**Events (N = 244)**
Pneumonia	2 (1.5)	2 (0.7)	6 (4.6)	6 (2.5)
Pulmonary Edema	1 (0.7)	2 (0.7)	2 (1.5)	2 (0.8)
Cardiovascular	17 (12.5)	26 (9.5)	17 (13.0)	19 (7.8)
Other	5 (3.7)	5 (1.8)	5 (3.8)	5 (2.0)
Myocardial infarction	2 (1.5)	2 (0.7)	5 (3.8)	5 (2.0)
Congestive heart failure	5 (3.7)	6 (2.2)	1 (0.8)	1 (0.4)
Hypotension	2 (1.5)	2 (0.7)	4 (3.1)	4 (1.6)
Arrhythmias	3 (2.2)	4 (1.5)	2 (1.5)	2 (0.8)
Tachycardia	3 (2.2)	3 (1.1)	1 (0.8)	1 (0.4)
Gastrointestinal	20 (14.7)	28 (10.2)	10 (7.6)	13 (5.3)
Other	6 (4.4)	9 (3.3)	4 (3.1)	5 (2.0)
Nausea/vomiting	8 (5.9)	8 (2.9)	1 (0.8)	2 (0.8)
GI Bleeding	5 (3.7)	5 (1.8)	3 (2.3)	3 (1.2)
Diarrhea	5 (3.7)	5 (1.8)	2 (1.5)	2 (0.8)
Genitourinary	15 (11.0)	20 (7.3)	15 (11.5)	15 (6.1)
Renal dysfunction/Acute Kidney Injury	11 (8.1)	13 (4.7)	15 (11.5)	15 (6.1)
Other	5 (3.7)	6 (2.2)	0 (0.0)	0 (0.0)
Other systemic disease/event	15 (11.0)	19 (6.9)	11 (8.4)	14 (5.7)
Other	9 (6.6)	9 (3.3)	2 (1.5)	2 (0.8)
Surgery – planned/elective	5 (3.7)	5 (1.8)	4 (3.1)	4 (1.6)
Pain (beyond anticipated pain post-surgery)	2 (1.5)	2 (0.7)	6 (4.6)	6 (2.5)
Surgery – emergency	3 (2.2)	3 (1.1)	2 (1.5)	2 (0.8)
Hematology	11 (8.1)	12 (4.4)	15 (11.5)	16 (6.6)
Anemia	2 (1.5)	2 (0.7)	6 (4.6)	6 (2.5)
Leukopenia	3 (2.2)	3 (1.1)	5 (3.8)	5 (2.0)
Malignancy	1 (0.7)	1 (0.4)	3 (2.3)	3 (1.2)
Other	3 (2.2)	4 (1.5)	1 (0.8)	1 (0.4)
Fluid Collection	11 (8.1)	14 (5.1)	9 (6.9)	11 (4.5)

	NMP n(%)		SCS n(%)	
Safety Event Type	**Patients (N = 136)**	**Events (N = 275)**	**Patients (N = 131)**	**Events (N = 244)**
Ascites	4 (2.9)	6 (2.2)	2 (1.5)	3 (1.2)
Pleural effusion	2 (1.5)	2 (0.7)	3 (2.3)	3 (1.2)
Abdominal collection	2 (1.5)	3 (1.1)	2 (1.5)	2 (0.8)
Extremities edema	2 (1.5)	2 (0.7)	1 (0.8)	1 (0.4)
Other	1 (0.7)	1 (0.4)	2 (1.5)	2 (0.8)
Neurology/Psychiatry	9 (6.6)	11 (4.0)	8 (6.1)	9 (3.7)
Altered mental status	4 (2.9)	4 (1.5)	3 (2.3)	4 (1.6)
Seizure	1 (0.7)	2 (0.7)	3 (2.3)	3 (1.2)
Stroke/TIA	3 (2.2)	3 (1.1)	0 (0.0)	0 (0.0)
Musculoskeletal	9 (6.6)	9 (3.3)	7 (5.3)	7 (2.9)
Other	8 (5.9)	8 (2.9)	7 (5.3)	7 (2.9)
Electrolyte abnormality	3 (2.2)	3 (1.1)	10 (7.6)	11 (4.5)
Hyperkalemia	3 (2.2)	3 (1.1)	8 (6.1)	9 (3.7)
Dermatologic	3 (2.2)	3 (1.1)	3 (2.3)	3 (1.2)
Other	3 (2.2)	3 (1.1)	1 (0.8)	1 (0.4)
Endocrinology	0 (0.0)	0 (0.0)	3 (2.3)	3 (1.2)
Hyperglycemia	0 (0.0)	0 (0.0)	3 (2.3)	3 (1.2)
TOTAL	95 (69.9)	275 (100.0)	93 (71.0)	244 (100.0)
Number of events in specific codes may not add up to the number of events for the corresponding system code since only system and specific codes that occurred in ≥ 1% of subjects were presented.				

The US WP01 clinical data shows a comparable total number of patients with SAEs and number of SAEs across study arms.

There was a higher incidence of hepatic incidences in the NMP arm compared to the SCS arm (24.7% and 19.3%, respectively). The incidence of anastomotic biliary stricture-related adverse events was higher in the NMP group (7.3%) than the SCS group (2.9%). Adverse events related to graft dysfunction were higher in the NMP group (5.1%) than the SCS group (2.9%). Despite a relatively low overall incidence rate, there was higher incidence of cholangitis in the NMP group than in the SCS group (1.8% versis 0.8%, respectively). Despite an overall low incidence rate, there was a higher proportion of ischemic cholangiopathy in the NMP arm (0.7%) than in the SCS arm (1.2%).

Table 13 provides information on reported liver incidents and device deficiencies by donor type. Device deficiencies include device failures, device malfunctions, and user errors. There were a total of two (2) liver incidents (due to livers discarded following transport) and fourteen (14) device malfunctions in the study.

Table 13: Liver Incidents and Device Deficiencies by Donor Type

	Overall # events (# subjects)		DBD # events (# subjects)		DCD # events (# subjects)	
Event	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Liver Incident	2 (2)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Device Failure (NMP Only)	0 (0)	-	0 (0)	-	0 (0)	-
Device Malfunction (NMP Only)	14 (14)	-	10 (10)	-	4 (4)	-
Use Error (NMP Only)	0 (0)	-	0 (0)	-	0 (0)	-

The two liver incidences involved donor liver AFEV307 and AFJ160. Donor liver AFEV307 was discarded due to "suboptimal perfusion parameters, " increased vascular resistance, and IVC collapse. Donor liver AFJZ160 was discarded due to progressively increasing levels of vascular resistance during perfusion. In addition to the above discarded livers, a third donor graft—Liver AGAW496—was discarded after perfusion due to the liver being unsuitable for transplant (80% macrovesicular steatosis in the first biopsy and 70% macrovesicular steatosis in the second biopsy). All three NMP livers discarded after transport were NMP-DBD livers. No livers in the SCS arm were discarded after transport.

The intended recipient of liver AFEV307 was returned to the waitlist and received a liver transplant outside of the study on May 26, 2018 and was reported by the site as doing well as of October 21, 2020. The intended recipient of liver AFJZ160 was returned to the waitlist, but did not receive another liver, as their health declined over the next couple of months. They were delisted from UNOS on December 24, 2018, as they were too sick to proceed with a transplant due to encephalopathy. They ultimately passed away in January 2019.

The recipient of liver AGAW496 was returned to the waitlist. They were later randomized to liver AGA2141 and completed the study successfully.

The review team considers grafts AFEV307 and AFJZ160 lost due to inadequate perfusion using the OrganOx *metra*® and suboptimal IVC canulation. Post-perfusion incidences such as these present potential risks to both the donor liver (via degraded graft quality, graft loss, and reduced utilization rates of NMP livers) and to the

selected recipient (such at those related to vascular access or a return to the transplant waiting list until another organ becomes available).

OrganOx reported 14 device malfunctions. Of the 14 device malfunctions, 12 occurred in livers that were transplanted. Of these 12 device malfunctions, 2 of these occurred during set up of the device (Livers AEJX212 and AELD404) while the liver was being retrieved from the donor and resulted in transport via cold storage. In both of these cases there was no delay or impact on CIT. These livers are excluded from the Per-Protocol analysis and analyzed as SCS livers in the As-Treated analysis. Both subjects experienced EAD.

There were 2 deaths in subjects that received a liver that experienced a device malfunction; Subject 06-008/Liver AEES037 died from recurrent hepatocellular carcinoma on Day 263 following transplant; and Subject 03-002/Liver AEFN041 died due to secondary hemorrhage from the hepatic artery on Day 9. There was no sequalae to the device malfunction in either case and both of these deaths have been judged by the independent CEC to be not related to the method of preservation.

The remaining 8 subjects that received a liver that experienced a device malfunction had no reported AEs or events.

Two device malfunctions occurred in livers that were not transplanted. One liver (AEFZ194) was not transplanted due to the subject not being eligible to proceed to transplant and 1 liver (AFJP423) was not transplanted because the DCD donor did not proceed to donation.

No device malfunctions occurred during transport or resulted in an emergency transfer to SCS. There were no graft losses in cases that encountered a device malfunction.

As evidenced by the above information, there is some risk to donor grafts perfused by the OrganOx *metra*® and intended recipients of those grafts. To reduce risks associated with device use, OrganOx introduced enhanced training for *metra*® operators to reduce the risk of device misuse or donor graft mishandling. This training, introduced in December 2018, featured best practices for bile duct cannulation with surgeons during in-person and remote support. This training involved the use of a different (monofilament) material in place of silk, ensuring that the correct tube size was matched to each bile duct, and that this was inserted to the correct depth within the bile duct. Subjects with anastomotic biliary strictures for both the NMP and SCS arms are presented for the As-Treated analysis population based on these enhanced training dates using a tertile analysis in **Table 14**. The rate of subjects with anastomotic biliary strictures reduced in the NMP arm over time, demonstrating continued improvement during the study with enhanced training and guidance on best practices contributing to the improvement. However, the Agency notes the possibility of other factors—such as surgeon comfort and experience after having performed multiple procedures with the OrganOx *metra*® System—as potential contributors of improved outcomes. The direct effect of enhanced training on clinical outcomes should be explored in a prospective manner.

Table 14: Enhanced Training Analysis – Anastomotic Biliary Strictures (As-Treated)

	Tertile 1 and 2		Tertile 3	
	NMP[1]	**SCS**	**NMP[1]**	**SCS**
Number of transplanted subjects	90	89	42	43
At risk at 12 months[2]	68	75	35	42
Subjects with events	15	8	3	0
Cumulative Incidence[3]	17.7%	9.2%	7.5%	0.0%
Standard error	4.2%	3.1%	4.2%	0.0%
95% CI	(11.0%, 27.7%)	(4.7%, 17.6%)	(2.5%, 21.6%)	(0.0%, 0.0%)

[1]Surgeons of two NMP subjects (Liver IDs: AFED332, AFLJ403) did not have a training date reported. Subject AFED332 had a transplant that occurred prior to Enhanced Training 2 and experienced a biliary stricture, therefore is included in the transplanted subjects in Tertiles 1 and 2. Subject AFLJ403 had a transplant that occurred after Enhanced Training 2 and did not experience a biliary stricture. Due to transplant timing, they are unable to be included in the transplanted subjects (would fall in either Tertile 2 or 3).
[2]Number of subjects at risk at the beginning of 12 months visit windows (335 days from procedure).
[3]Estimates made at scheduled visit days (365 days from procedure).
Tertile 1 and 2: Transplant performed before the completion of Enhanced Training 1 and/or Enhanced Training 2
Tertile 3: Transplant performed after the completion of both Enhanced Training 1 and Enhanced Training 2

Table 15 presents the SAEs by randomization group at the study follow-up visits. There were no notable differences in the incidence of SAEs between the two randomization arms overall. There were no unanticipiated device effects (UADEs) reported in this study.

Table 15: SAEs per Randomization Group at Study Timepoints

		Overall # events (# subjects)	
	ALL	**NMP**	**SCS**
Serious Adverse Event	519 (188)	275 (95)	244 (93)
Serious Adverse Event (Procedure- related)[1]	442 (174)	232 (87)	210 (87)

		Overall # events (# subjects)	
	ALL	**NMP**	**SCS**
Serious Adverse Event (Device- related)[2]	80 (47)	80 (47)	-
[1]Procedure-related events include those events categorized as either probabl not, possibly, probably, or definitely related to the procefure. [2]Device-related events include those events categorized as either probably not, possibly, probably, or definitely related to the device. Discharge events include events orccuring on or prior to discharge or events where a discharge date was not reported.			

Safety Results Summary

The analysis of safety was based on the ITT cohort of 136 NMP and 131 SCS enrolled subjects. All adverse events reported for a subject—regardless of the duration of time in the study—are included through a subject's exit from the site. If a cohort other than ITT was presented, this is noted in the title of the table.

Twelve-month graft survival rates were 97.0% and 97.7% in the NMP and SCS arms, respectively; rates were considered comparable across arms. Patient survival was numerically worse with NMP as compared with SCS (92.5% and 96.6%, respectively), but both the applicant and Agency's adjudication of these cases do not suggest that the device was directly responsible for the increased rates of patient deaths with the NMP arm. The Agency also notes that the study was not powered to detect differences in patient survival.

There was a higher incidence of hepatic incidences in the NMP arm compared to the SCS arm. The incidence of anastomotic biliary stricture-related adverse events was higher in the NMP group than the SCS group. Adverse events related to graft dysfunction were higher in the NMP group than the SCS group. Despite a relatively low overall incidence rate, there was a higher incidence of cholangitis and ischemic cholangiopathy in the NMP group than in the SCS group.

OrganOx attempted to address the higher incidence of biliary strictures and graft dysfunction in the NMP arm relative to the SCS arm via the introduction of enhanced training during the WP01 study. While the Agency recognizes the higher rate of cholangitis and ischemic cholangiopathy in the NMP arm relative to the SCS arm, the overall rates of both were low between arms. A review of the available patient mortality, graft survival, and SAE data revealed no safety-related concerns beyond those already described. The remaining reported adverse events are typical following liver transplantation.

2. Effectiveness Results

Primary Endpoint
The analysis of effectiveness was based on 136 evaluable patients from the NMP cohort and 130 from the SCS cohort at the 12-month time point. Key effectiveness outcomes are presented in **Tables 16** to **18**.

Table 16: Early Allograft Dysfunction – ITT, Per-Protocol, and As-Treated Analysis Populations

	NMP*	SCS	Superiority P-value
ITT Analysis Primary Endpoint[1]			
Analysis Population	N=136	N=130	
Number of subjects with incomplete EAD information requiring imputation	N=9	N=3	
EAD Prior to Imputation	20.5% (26/127)	22.8% (29/127)	
EAD using imputation[2]	20.6% (14.5%, 28.5%)	23.7% (17.1%, 31.9%)	0.275
Per-Protocol Analysis[3, 4]			
Analysis Population	N=133	N=130	
Number of subjects with incomplete EAD information requiring imputation	N=9	N=3	
EAD Prior to Imputation	18.5% (23/124)	22.8% (29/127)	
EAD using imputation[2]	18.6% (12.7%, 26.4%)	23.8% (17.2%, 31.9%)	0.158
As-Treated Analysis[3, 4]			
Analysis Population	N=133	N=132	
Number of subjects with incomplete EAD information requiring imputation	N=9	N=3	
EAD Prior to Imputation	18.5% (23/124)	24.0% (31/129)	

	NMP*	SCS	Superiority P-value
EAD using imputation[2]	18.7% (12.8%, 26.5%)	24.9% (18.2%, 33.1%)	0.115

*Three subjects (AFJX183, AGJY324, AECG396) were identified as having elevated day 7 INR values due to anticoagulation. Day 7 INR values
for these 3 subjects were therefore considered missing, and imputed to determine EAD status.
[1]ITT Population
[2]Multiple imputation was used for subjects with missing lab values that were required to determine EAD status. Imputation was not used to determine EAD status when: i) the subject already had one or more lab values meeting EAD criteria; ii) the subject had been discharged prior to day 7 with lab values below EAD threshold; or iii) the subject had last available INR values and available follow-up INR values below EAD threshold with no reported hospital re-admissions.
[3]One subject (AGBX122) was excluded from the analysis due to exclusion criteria being met.
[4]Two subjects (AEJX212, AELD404) received livers that were randomized to the NMP arm but were not placed on the device and instead were
transported using cold storage. These subjects are excluded from the Per-Protocol Analysis and included in the SCS arm in the As-Treated Analysis.

Table 16 shows the results of the primary endpoint for the ITT, Per-Protocol, and As-Treated populations. EAD rates both prior to and following imputation are included, and the 1-sided superiority p-values are presented (a non-inferiority analysis was not pre-specified). Adjustment for participating (recipient) center was pre-specified in the SAP for the primary analysis of the imputed data. However, due to convergence issues, a logistic model that did not adjust for participating (recipient) center was used.

As an additional sensitivity analysis, EAD was also assessed using multiple imputation to impute missing lab values to determine EAD status for subjects discharged from the hospital prior to Day 7 and/or subjects with available early INR values below the EAD threshold. In the primary analysis these subjects were considered not to have EAD. As in the primary analysis, multiple imputation was also used for subjects where EAD status was unable to be confirmed by complete labs or at least 1 lab value meeting criteria for EAD. Sensitivity analyses were conducted to demonstrate the impact on primary endpoint results using multiple imputation for EAD status that is unable to be confirmed by complete labs or at least 1 lab value meeting criteria for EAD. The results of this sensitivity analysis are presented in **Table 17**. EAD rates using imputation are similar to the ITT analysis in both the NMP and SCS arms (21.4% and 25.6%, respectively; p-value=0.218).

Table 17: Early Allograft Dysfunction – Sensitivity Analysis

	NMP*	SCS	Superiority P-value
Sensitivity Analysis[1]			
Analysis Population	N=136	N=130	
Number of subjects with incomplete EAD information requiring imputation	N=19	N=14	
EAD Prior to Imputation	22.2% (26/117)	25.0% (29/116)	
EAD using imputation[2, 3]	21.4% (15.1%, 29.5%)	25.6% (18.7%, 34.1%)	0.218

*Three subjects (AFJX183, AGJY324, AECG396) were identified as having elevated day 7 INR values due to anticoagulation. Day 7 INR values for these 3 subjects were therefore considered missing, and imputed to determine EAD status.
[1]ITT Population
[2]Multiple imputation was used in the Sensitivity Analysis to impute missing lab values to determine EAD status for subjects discharged from hospital prior to day 7 and/or subjects with available INR values below the EAD threshold. In the Primary Analysis these subjects were considered not to have EAD.
[3]As in the Primary Analysis, multiple imputation was also used for subjects where EAD status is unable to be confirmed by complete labs or at least 1 lab value meeting criteria for EAD.

In addition to the primary endpoint analysis of EAD by randomization arm, results were also summarized by donor type. The EAD rates by donor type and randomization arm are presented in **Table 18** for the ITT, Per-Protocol, and As-Treated analysis populations.

Table 18: Early Allograft Dysfunction by Donor Type – ITT, Per-Protocol, and As-Treated Analysis Populations

	DBD		DCD	
	NMP*	SCS	NMP	SCS
ITT Analysis[1]				
Analysis Population	N=114	N=114	N=22	N=16
Number of subjects with incomplete EAD information requiring imputation	N=8	N=2	N=1	N=1
EAD Prior to Imputation	18.9% (20/106)	20.5% (23/112)	28.6% (6/21)	40.0% (6/15)
EAD using imputation[2]	18.7% (12.5%, 27.2%)	21.3% (14.7%, 29.8%)	30.1% (14.5%, 52.4%)	41.0% (19.8%, 66.0%)
Per-Protocol Analysis[3, 4]				
Analysis Population	N=113	N=114	N=20	N=16

	DBD		DCD	
	NMP*	**SCS**	**NMP**	**SCS**
Number of subjects with incomplete EAD information requiring imputation	N=8	N=2	N=1	N=1
EAD Prior to Imputation	18.1% (19/105)	20.5% (23/112)	21.1% (4/19)	40.0% (6/15)
EAD using imputation[2]	17.9% (11.8%, 26.4%)	21.3% (14.7%, 29.9%)	22.3% (8.8%, 46.2%)	41.1% (19.9%, 66.1%)
As-Treated Analysis[3, 4]				
Analysis Population	N=113	N=115	N=20	N=17
Number of subjects with incomplete EAD information requiring imputation	N=8	N=2	N=1	N=1
EAD Prior to Imputation	18.1% (19/105)	21.2% (24/113)	21.1% (4/19)	43.8% (7/16)
EAD using imputation[2]	17.9% (11.8%, 26.4%)	22.0% (15.3%, 30.5%)	22.8% (9.1%, 46.6%)	44.6% (23.1%, 68.3%)

*Three DBD subjects (AFJX183, AGJY324, AECG396) were identified as having elevated day 7 INR values due to anticoagulation. Day 7 INR values for these 3 subjects were therefore considered missing, and imputed to determine EAD status.
[1]ITT Population
[2]Multiple imputation was used for subjects with missing lab values that were required to determine EAD status. Imputation was not used to determine EAD status when: i) the subject already had one or more lab values meeting EAD criteria; ii) the subject had been discharged prior to day 7 with lab values below EAD threshold; or iii) the subject had last available INR values and available follow-up INR values below EAD threshold with no reported hospital readmissions.
[3]One DCD subject (AGBX122) was excluded from the analysis due to exclusion criteria being met.
[4]One DBD subject (AEJX212) and one DCD subject (AELD404) received livers that were randomized to the NMP arm but were not placed on the device and instead were transported using cold storage. These subjects are excluded from the Per-Protocol analysis and included in the SCS arm in the As-Treated analysis.

The WP01 pivotal trial's primary analysis was designed around the hypothesis that EAD rates following transplant of livers preserved with NMP would be superior to (lower than) EAD rates following transplant of livers preserved with SCS. The study was designed to demonstrate a reduction in EAD rates from 25% in the SCS arm to 10% in the NMP arm.

The superiority endpoint was not met for the primary endpoint. In the ITT analysis, the NMP arm had a lower imputed EAD rate than the SCS arm (20.6% and 23.7%, respectively; p-value=0.275). Imputed rates of EAD in the As-Treated NMP and SCS cohorts were 18.7% and 24.9%, respectively (p=0.115).

Subgroup analysis by donor type showed a numerically lower incidence of EAD observed in the DBD-NMP arm as compared to the DBD-SCS arm, 17.9% NMP versus 22.0%, respectively. In subjects with DCD liver transplants, the incidence of EAD was 22.8% in the DCD-NMP group versus 44.6% in the DCD-SCS group (per

the As-Treated analysis following imputation). However, the number of patients in these subgroups were limited (19 in the DCD-NMP group; 16 in the DCD-SCS group) and the study was not powered to measure the significance of this effect.

In conclusion, superiority was not met for primary endpoint. Nonetheless, there was a numerically lower incidence of EAD observed in the NMP arm compared to SCS arm, and the more pronounced lower incidence of EAD in the DCD-NMP group compared to the DCD-SCS group.

The numerically lower incidence of EAD in the NMP arm as compared to the SCS arm does not correlate with clinically significant improvements in graft and patient survival and other clinically relevant outcomes. However, we consider the EAD rates clinically comparable between the DBD-NMP and DBD-SCS arms. The clinical data also suggests a potential benefit of DCD organs preserved via NMP compared to DCD organs preserved by SCS. However, this observation is best confirmed via additional clinical studies appropriately powered to evaluate this effect.

Effect of Enhanced Training

Early in the US WP01 pivotal study, there was a concern regarding a higher incidence of EAD in the NMP arm compared to SCS. In previous communication with the Agency, OrganOx attributed these outcomes largely to improper cannulation technique and back-table suturing. To address these challenges, OrganOx implemented enhanced training related to use of the device and with a particular focus on cannulation. This program consisted of further video and on-site training from the OrganOx Clinical Field Specialists. In particular, attention was paid to the technique for the placement and securing of the vascular cannulas. At the same time, OrganOx changed the training sign-off such that individual surgeons were required to be certified as trained by the specialists. This differed from the previous practice, which required that institutions (not individuals) were required to be signed-off.

Training occurred between March and May of 2018 as described in **Figure 4** below:

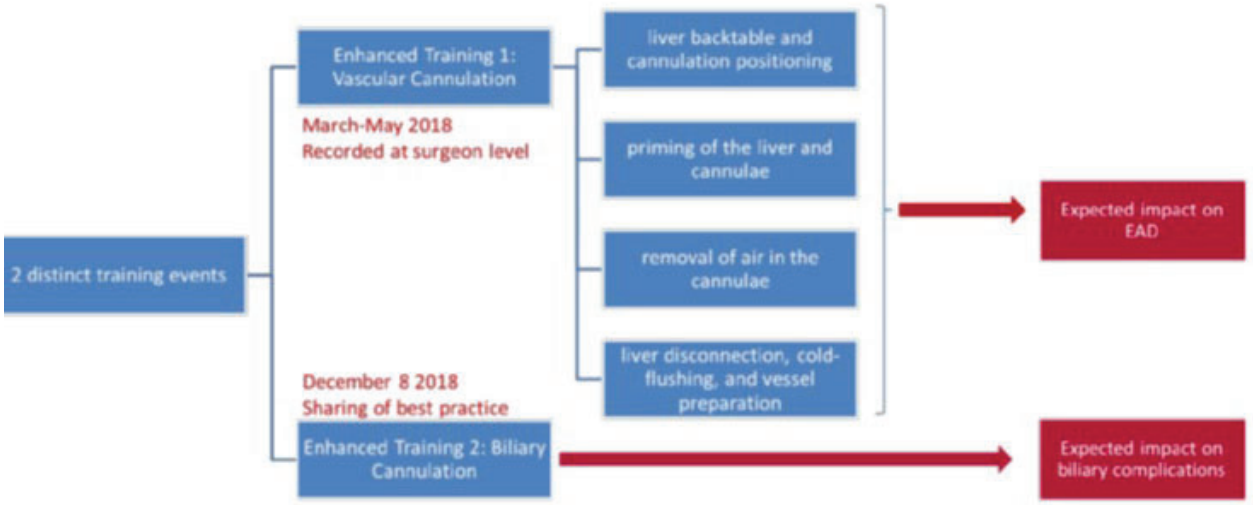

Figure 4: OrganOx Enhanced Training Timeline

EAD rates (unimputed) for both the NMP and SCS arms are presented for the As-Treated analysis population before and after enhanced surgeon training in **Figure 5** and **Table 19**. EAD rates in the NMP arm decreased after enhanced training (23.5% before enhanced training as compared to 14.1% after enhanced training), while the rates were similar pre- and post-enhanced training in the SCS arm (21.3% before enhanced training and 25.6% after enhanced training). The incidence of EAD following these changes was lower in the NMP arm than before the enhanced training, whereas the incidence of EAD in the SCS arm showed no such change.

Table 19: Enhanced Training Analysis – Early Allograft Dysfunction (As-Treated)

	Early Allograft Dysfunction (EAD) by Enhanced Training 1 Timing	
Randomization Arm	**Prior to Enhanced Training [1] Completion by Surgeon**	**After Enhanced Training [1] Completion by Surgeon**
NMP[1]	23.5% (12/51)	14.1% (10/71)
SCS[2]	21.3% (10/47)	25.6% (21/82)
EAD is a binary outcome defined by the presence of one of the following 3 outcomes: 1. Serum bilirub in ≥ 10 mg/dL at day 7 post-transplant; 2. International normalized ratio ≥ 1.6 at day 7 post-transplant; 3. ALT or AST > 2000 IU/L within the first 7 days post-transplant. Additional clinically justified decision rules were implemented if EAD status was unable to be confirmed by complete labs or at least 1 lab value meeting criteria for EAD. [1]Surgeons of two NMP subjects (Liver IDs: AFED332, AFLJ403) did not have a training date reported. Therefore, these 2 subjects are not included in this analysis. An additional 9 subjects had incomplete EAD information and are not included. [2]Three subjects had incomplete EAD information and are not included in this analysis.		

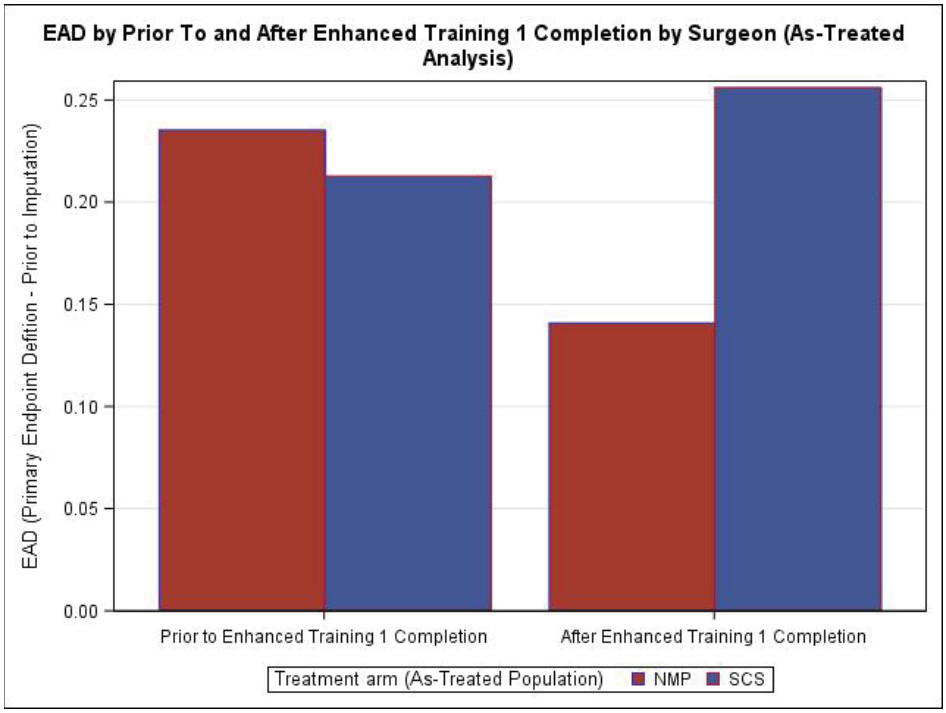

Figure 5: EAD by Pre- and Post-Enhanced Training Completion at Sites (As-Treated)

Potential improvements were also evaluated as a function of how much enhanced training each person had received. Surgeons were divided into one of three "tertiles" reflecting the extent of their training. The number of NMP liver transplants transplanted by surgeons in these tertiles are stated in parentheses:

- First Tertile: Transplants performed before the completion of both Enhanced Training 1 and 2 (52 NMP cases).
- Second Tertile: Transplants performed after the completion of either Enhanced Training 1 or 2 (37 NMP cases).
- Third Tertile: Transplants performed after the completion of both Enhanced Training 1 and 2 (42 NMP cases)

Table 20: Enhanced Training Analysis – Serious Anastomotic Biliary Strictures (As-Treated)

	Serious Biliary Strictures (anastomotic) by Enhanced Training Timing		
Randomization Arm	**First Tertile**	**Second Tertile**	**Third Tertile**
NMP	9	5	1

SCS	1	3	0
Cutoffs between tertiles correspond to the following: First and Second Tertile (March-May 2018): Date that site signed off as completing review of training videos relating to "backtable and cannulation positioning" and "liver disconnection and vessel preparation" Second and Third Tertile (08DEC2018): Date OrganOx began to share revised best practice for bile duct cannulation with surgeons during in-person/remote support, including the use of a monofilament suture. The choice of suture material and technique used was discussed with the surgeon and recorded			

As demonstrated in **Table 20**, the rate of anastomotic biliary strictures in the NMP arm demonstrated continued improvement throughout the study. The decrease in EAD rates in the NMP arm after enhanced training was noted, but whether improved outcomes were a direct result of the enhanced training has not been definitively established due to a number of unknowns: for instance, there were not enough preservation events involving either cannula misplacement or suspected air entrainment to establish a relationship between the occurrence of these events and subsequent EAD events. The Agency notes that it would be difficult to establish a relationship between cannula misplacement or suspected air entrainment events and subsequent EAD events in general, regardless of the number of either type of incident. Therefore, improving upon cannualation and suturing techniques may or may not have contributed to reduced rates of EAD. Finally, it is intuitive to the Agency that improvements may have come from the fact that surgeons became more familiar with and comfortable using the OrganOx *metra*® after multiple such uses, rather than as a consequence of the enhanced training. However, the reduction of EAD rates after enhanced training presents some evidence of its potential benefit. Definitive conclusions on the effect of enhanced training on clinical outcomes should be further explored in a controlled, prospective manner.

Secondary Endpoints:
Note that none of these secondary endpoints underwent formal hypothesis testing.

1. **To compare graft and subject survival between NMP and SCS livers:** There were seven (7) graft failures (four (4) in the NMP arm and three (3) in the SCS arm). Graft failures included primary non-function (PNF), any instances of re-transplant during the follow-up period, and any deaths due to graft failure.

   Graft survival at 12 months was 97.0% (95% CI: 92.1%, 98.9%) and 97.7% (95% CI: 93.0%, 99.2%) in the NMP and SCS groups, respectively. 2019 OPTN/SRTR data show national graft survival rates with SCS at 12-months post-transplant as 91.1%. The graft survival data in both arms of this trial trend favorably with the national average.

   Subject survival at 12 months were 92.5% (95% CI: 86.6%, 95.9%) and 96.6% (95% CI: 91.3%, 98.7%) in the NMP and SCS arms, respectively. While there

was a numerical difference in the number of deaths between the randomization arms, no deaths were adjudicated as related to the *metra*® device. 2019 OPTN/SRTR data show national subject survival rates with SCS at 12-months post-transplant as 92.6%. The results indicate that subject survival using the OrganOx *metra*® device was in line with the national average.

The US trial was not powered to test patient and graft survival; however, it was expected that a lower incidence of EAD and graft injury would correlate with improved graft survival, lower biliary complication rate at one year, and shorter hospital stay after transplant. The expected correlations were not observed.

2. **To compare evidence of post-reperfusion syndrome between NMP and SCS livers on transplantation:** Post-reperfusion syndrome (PRS) is a serious complication of liver transplantation presenting as hemodynamic instability within a few minutes of reperfusion of the transplanted organ, often in association with metabolic, electrolyte, and coagulation abnormalities. PRS marks a time of extreme risk to frail patients, particularly those with restricted physiological reserve. In such patients, PRS may lead to irreversible cardiovascular decompensation, including cardiac arrest on the operating table.

   In the WP01 US IDE trial, the occurrence of post-reperfusion syndrome decreased from 14.6% in the SCS arm to 5.9% in the NMP arm. While lower rates of post-reperfusion syndrome were seen in the NMP group compared to the SCS group overall, the difference was most pronounced in DBD livers (4.4% NMP vs. 14.0% SCS).

   While decreasing PRS rates is a potential clinical benefit which may impact the management of surgically complex or medically high-risk patients, the WP01 IDE study did not include recipients in an extremely friable condition. Friability was not evaluated, and MELD scores were comparatively low (the mean calculated MELD score for the DCD-NMP recipients and DCD-SCS recipients was 17.27 and 20.25, respectively). Patients in this study were not considered to be among the sickest patients awaiting transplantation. Additionally, the lower incidence of PRS in the NMP arm did not decrease graft loss or patient deaths. As a result of the above outocomes, the potential clinical benefit of decreasing PRS rates was not demonstrated in the WP01 IDE study.

3. **To compare biochemical liver function between NMP and SCS livers.** There were differences in the first 7 days post-operatively between the NMP and SCS arms with lower median levels of AST, ALT, and creatinine in the NMP arm (**Tables 21-24**).

Table 21: Biochemical Liver Function Assessments: AST, ALT and Creatinine

Biochemical test*	NMP	SCS	p-value**
AST (IU/L)			
Day 1-7 N	162.2 (101.3, 332.8) 136	200.7 (141.4, 349.4) 129	0.032
ALT (IU/L)			
Day 1-7 N	215.9 (113.9, 349.7) 136	268.6 (169.9, 457.9) 129	0.009
Creatinine (mg/dL)			
Day 1-7 N	1.2 (0.9, 1.6) 135	1.4 (1.0, 1.8) 129	0.047
*Median and interquartile range displayed for each treatment group. **P-value calculated from a Mann-Whitney test			

Table 22: Peak AST by Randomization Arm and Donor Type

	Overall				DBD				DCD			
	NMP		SCS		NMP		SCS		NMP		SCS	
	N	Geometric Mean[3] (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)
Peak AST - Any AST lab(s) available in first 7 days	136	540.3 (453.3, 644.1)	129	722.4 (609.0, 857.0)	114	528.8 (439.1, 636.8)	114	653.7 (548.9, 778.5)	22	604.2 (352.5, 1035.7)	15	1543.8 (904.0, 2636.4)
Peak AST - Day 1 AST available[1]	133	538.1 (450.8, 642.4)	129	722.4 (609.0, 857.0)	112	519.6 (430.8, 626.6)	114	653.7 (548.9, 778.5)	21	649.2 (376.5, 1119.3)	15	1543.8 (904.0, 2636.4)
Peak AST - At least 2 AST labs available[2]	135	540.3 (452.7, 644.8)	129	722.4 (609.0, 857.0)	113	528.6 (438.2, 637.7)	114	653.7 (548.9, 778.5)	22	604.2 (352.5, 1035.7)	15	1543.8 (904.0, 2636.4)

[1]Day 1 is often the peak AST observed
[2]COPE Study used this definition
[3]Geometric mean values are in units of IU/L

Table 23: Peak ALT by Randomization Arm and Donor Type

	Overall				DBD				DCD			
	NMP		SCS		NMP		SCS		NMP		SCS	
	N	Geometric Mean[1] (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)
Peak ALT - Any ALT lab(s) available in first 7 days	136	381.8 (326.4, 446.5)	129	500.9 (432.7, 579.8)	114	374.7 (316.4, 443.7)	114	464.6 (397.4, 543.1)	22	420.6 (270.4, 654.4)	15	887.3 (642.9, 1224.8)
Peak ALT - Day 1 ALT available	133	378.0 (322.9, 442.6)	129	500.9 (432.7, 579.8)	112	368.1 (310.7, 436.0)	114	464.6 (397.4, 543.1)	21	435.8 (275.5, 689.3)	15	887.3 (642.9, 1224.8)
Peak ALT - At least 2 ALT labs available	135	382.1 (326.3, 447.4)	129	500.9 (432.7, 579.8)	113	375.0 (316.2, 444.8)	114	464.6 (397.4, 543.1)	22	420.6 (270.4, 654.4)	15	887.3 (642.9, 1224.8)

[1]Geometric mean values are in units of IU/L

Table 24, Peak transaminase levels > 2000 IU/L during first 7 days post-operatively

	NMP patients	NMP Events	SCS patients	SCS events
ALT or AST > 2000 IU/L	5 (3.7)	5 (1.8)	4 (3.1)	4 (1.6)

Peak transaminase levels during first 7 days post-transplantation was evaluated as a direct measurement of hepatocellular injury. Among NMP recipients, there was a 25% lower peak AST level during the first 7 days as compared to SCS recipients (540 IU/L versus 722 IU/L), with a greater difference seen in the NMP-DCD recipients compared to DCD-SCS recipients (604 IU/L versus 1544 IU/L) – a reduction of 61% (**Table 22**). A similar effect was displayed in NMP liver recipients with respect to peak ALT levels. ALT levels were 24% lower in the NMP-DCD cohort and 53% lower in the NMP-DBD cohort as compared to SCS-DBD and SCS-DCD liver recipients, respectively.

These analyses support a reduced hepatocellular injury after reperfusion in the NMP group compared to SCS. However, the highest mean AST peak levels in the SCS and NMP groups were significantly below 2000 IU/L. The number of patients with peak AST > 2000 IU/L, a well-established and relevant clinical criterion for EAD, was similar across the NMP and SCS arms.

Because of the small DCD subgroup population and lack of correlation with other clinically relevant endpoints, lower AST peak levels in the NMP group as compared to the SCS group should be interpreted with caution and considered to be of no clinical importance.

4. **To compare evidence of ischemia-reperfusion injury between NMP and SCS livers:** There were no notable differences in the degree of ischemia reperfusion injury in liver biopsies between arms. There was a small, but notable difference in the proportion of livers with mild/moderate/severe lobular inflammation when comparing the post reperfusion to pre-storage biopsies between the arms. In the NMP arm, there was a 26.5% increase between pre-storage (52.4%) and post-reperfusion (78.9%) biopsies, whereas in the SCS arm there was a 44.7% increase between pre-storage (43.1%) and post-reperfusion (87.8%) biopsies.

   In summary, post-reperfusion ischemia-reperfusion injury was comparable across arm and most of the cases showed minimal grade (80%). Similarly, the incidence of lobular inflammation post reperfusion was also comparable across arms. The degree of inflammation was also comparable across arms. Approximately 40% of the cases were mild and approximately 40% were moderate/severe.

   These results are considered comparable across arms and were not reflected in relevant clinical outcomes.

5. **To compare evidence of biliary complications between NMP and SCS livers.** Biliary investigations and interventions between Day 7 and Month 6 were analyzed as a surrogate for biliary complications. Slightly lower rates of biliary investigations and interventions were observed in the NMP arm. Biliary investigations occurred in 11.0% (14/127) of NMP subjects and 12.7% (16/126) SCS subjects. Biliary interventions were reported for 9.4% (12/127) and 8.7% (11/126) of NMP and SCS subjects, respectively. However, biliary complications (mainly biliary anastomotic strictures), decreased from 9 cases in the first tertile to 1 case after the second enhanced training focusing on bile duct canulation in the NMP arm.

6. **To assess the feasibility and safety of the NMP as a method of organ storage and transportation.** There was a small difference between arms: thirty-one (31) subjects in the NMP arm and thirty-three (33) subjects in the SCS arm experienced at least one of the following: EAD, discard of a retrieved liver, or primary non-function.

7. **To compare organ utilization between NMP and SCS livers.** There were similar rates of livers randomized but not transplanted in NMP and SCS livers for DBD donors (NMP 20.3%; SCS 20.8%). There were more SCS than NMP livers randomized but not transplanted for DCD donors (NMP 55.1%; SCS 66.0%).

   However, the Agency notes that 30% (116/383) of randomized organs were excluded from the study. Seventy-eight percent of the excluded organs (90/116) were considered unsuitable for retrieval. In two cases, the livers were procured and subsequently excluded due to steatosis. These two cases were accepted by another transplant center and transplanted outside of the study. This indicates that the selection criteria in the US IDE study may potentially limit utilization of marginal and sub-optimal donors' organs.

Ten of the 116 (8.6%) excluded organs from the study were transplanted outside of the study. Six of these organs were not transplanted because the recipient was not eligible to proceed with the transplant and were reallocated outside the study. In two additional exclusions, the recipient withdrew consent.

The study did not include stratification to ensure similar enrollment across DCD arms, and there was a small number of DCD cases in the study. Therefore, the difference in randomized but not transplanted organs among DCD groups should be considered with caution.

8. **To assess the health economic implications of normothermic liver perfusion.** The median length of ICU stay after transplant was lower in the NMP (2 days) compared to the SCS arm (3 days). The median total length of hospital stay was the same in both treatment arms (9days).

Effectiveness Results Summary

Primary Endpoint
The analysis of effectiveness was based on 136 NMP and 130 SCS transplanted subjects. The endpoint included information through 7 days post-transplant; however, the primary analysis was based on imputed data therefore all 266 transplanted subjects were included in the primary analysis for effectiveness.

The WP01 study did not meet the pre-specified superiority EAD primary endpoint.

The incidence of EAD was numerically lower in the normothermic machine perfusion (NMP) arm (20.6%) compared to static cold storage (SCS) arm (23.7%) in the modified Intent-to-Treat (mITT) analysis. The numerically lower incidence of EAD in the NMP arm as compared to the SCS arm did not correlate with clinically significant improvements in graft and patient survival or other clinically relevant outcomes.

Secondary Endpoints
Peak transaminase levels during the first 7 days post-operatively were evaluated as a direct measurement of hepatocellular injury. Among NMP recipients, there was a 25% lower peak AST level during the first 7 days in the NMP group as compared to SCS recipients (540 IU/L versus 722 IU/L, respectively), with a greater difference seen in the NMP-DCD recipients compared to DCD-SCS recipients (604 IU/L versus 1544 IU/L) – a reduction of 61%.

These results should be interpreted cautiously, as the highest mean AST peak levels in the SCS arm were significantly below 2000 IU/L, a well-established clinically relevant criterion for EAD. Any improvements in AST levels in the NMP arm relative to the SCS arm were numerical and not clinically meaningful, nor hypothesis tested. Additionally, the small number of DCD cases and lack of correlation of lower

AST peak values in the NMP group with other clinically relevant endpoints was noted when evaluating potential improvements in the NMP arm over the SCS arm.

In the WP01 US IDE trial, there was a marked difference in the incidence of PRS across arms (14.6% versus 5.9% in the SCS and NMP arm, respectively). However, there was no correlation with the expected increase in mortality and primary non-function rates in the SCS as compared to the NMP arm. Therefore, the potential clinical benefits derived from decreasing PRS rates were not demonstrated in the WP01 IDE study.

Improvement in renal function in the early post-operative period, defined as a reduction in the median level of creatinine during the first seven days post-operatively (NMP 1.2 mg/dL; SCS 1.4 mg/dL), is considered of no clinical relevance.

In the WP01 IDE study, the mean preservation time was 554 minutes (9.2 hrs.) in the NMP arm compared to 317 minutes (5.2 hrs.) in the SCS arm. The mean preservation time in the SCS group was lower compared to the reference CIT (6-7 hours), considered acceptable and within the current clinical US practice standards, showing no risks for increasing the incidence of EAD, graft loss, or patient death[10]. The preservation time in the NMP arm (9.2 hrs.), compared to a safe SCS-CIT reference value of <7 hours CIT, only accounts for 2 extra hours of preservation time extension. Even though we consider this a promising finding, further studies are necessaryto achieve a clinically relevant extension in preservation time.

3. Exploratory Subgroup Analyses

A donor risk index is a score applied to donor grafts and is intended to help predict graft quality and relative risk of graft failure. A DRI score is a function of several donor parameters that have been identified as relative risk factors for poor outcomes, including age, steatosis, DCD donation, split livers, and prolonged cold ischemia time (>12 hours). Grafts with a higher DRI (≥1.9) have higher relative risks of allograft failure than those with lower DRI scores.

EAD (unimputed) events were explored across different ranges of DRI. Using the observed data, EAD by randomization arm is presented in the DRI quartiles of the study in **Table 25**. In the lower quartiles of DRI, EAD rates were similar between the randomization arms. The largest difference between the arms was observed in the highest quartile of DRI (19.2% EAD rate in the NMP arm and 33.3% in the SCS arm).

Table 25: Early Allograft Dysfunction by Donor Risk Index

	Donor Risk Index (DRI)							
	DRI ≤ 1.404948		1.404948 < DRI ≤ 1.622325		1.622325 < DRI ≤ 1.870489		DRI > 1.870489	
	NMP	SCS	NMP	SCS	NMP	SCS	NMP	SCS
Early Allograft Dysfunction (EAD)	25.0% (10/40)	25.7% (9/35)	17.6% (6/34)	19.4% (7/36)	18.5% (5/27)	15.6% (5/32)	19.2% (5/26)	33.3% (8/24)
EAD is a binary outcome defined by the presence of one of the following 3 outcomes: 1. Serum bilirubin ≥ 10 mg/dL at Day 7 post-transplant; 2: International normalized ratio ≥ 1.6 at Day 7 post-transplant; 3. ALT or AST > 2000 IU/L within the first 7 days post-transplant. Additional clinically justified decision rules were implemented if EAD status was unable to be confirmed by complete labs or at least 1 lab value meeting criteria for EAD.								

An analysis of EAD rates (unimputed) against the observed time on pump was performed for livers in the NMP arm. **Table 26** shows EAD rates vs. time on pump tertiles. There was no correlation between time on pump and observed EAD rates.

Table 26: Early Allograft Dysfunction by Time on Pump (NMP arm)

	Time on Pump Tertiles		
	Low (≤288 minutes)	Intermediate (288 < time on pump ≤381 minutes)	High (>381 minutes)
Early Allograft Dysfunction (EAD)	14.3% (6/42)	26.2% (11/42)	17.5% (7/40)
Chi-square test comparing EAD proportions between time on pump tertiles: p=0.3612 EAD is a binary outcome defined by the presence of one of the following 3 outcomes: 1. Serum bilirubin ≥ 10 mg/dL at day 7 post-transplant; 2. International normalized ratio ≥ 1.6 at Day 7 post-transplant; 3. ALT or AST > 2000 IU/L within the first 7 days post-transplant. Additional clinically justified decision rules were implemented if EAD status was unable to be confirmed by complete labs or at least 1 lab value meeting criteria for EAD.			

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

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning

the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 15 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

COPE WP02 Study

A. Study Design

The Consortium for Organ Preservation in Europe (funded by a European Union 7th Framework Program grant) sponsored the COPE WP02 Clinical Trial "A multicenter randomized controlled trial to compare the efficacy of *ex-vivo* normothermic machine perfusion with static cold storage in human liver transplantation." The COPE Trial was an investigator-led, multinational, open-label, two-arm randomized trial at 7 sites in England, Belgium, Spain and Germany. Approval was obtained from national research ethics committees and medical device regulatory bodies in each trial region.

Livers from adult DBD and DCD certification of death were randomly assigned 1:1 between the OrganOx *metra*® system and SCS as the method of preservation. Inclusion criteria for donors and recipients were deliberately broad to represent the full spectrum of clinical practice. Whole livers from DBD and DCD (Maastricht category III)[2] donors aged at least 16 years were eligible. Recipients were eligible provided they were at least 18 years old and listed for a liver-only transplant, excluding those with fulminant liver failure, due to their poor prognosis regardless of organ quality. Once an eligible donor organ was allocated to a consented recipient and the availability of the NMP team was confirmed, the liver was randomized. All clinical decisions thereafter, including graft suitability and procedure scheduling, were made independently of the trial team.

Using an online randomization tool, livers were assigned to NMP or SCS with 1:1 allocation ratio as per a computer-generated randomization schedule using variable block size, stratified by transplant center and donor type (DBD/DCD). Livers randomized to SCS were retrieved, preserved, transported and transplanted according to local standard practice. Following randomization to NMP, the OrganOx *metra*® and a member of the research team were transported to the donor hospital. The donor organ was retrieved and cannulated, the device was setup and the organ was connected to the device according to the Instructions for Use. Once the liver was connected to the OrganOx *metra*®, perfusion commenced and NMP continued throughout the duration of transport and storage until the transplanting team were ready to implant the liver. The protocol stipulated NMP duration was 4-24 hours.

The primary objective of the study was to compare the effect of NMP to SCS in the prevention of preservation injury and graft dysfunction, as measured by peak transaminase levels in the first week following transplantation. The primary endpoint was defined as the difference in peak AST within 7 days post-transplant between the two treatment arms. OrganOx elected to use early post-transplant peak-AST as the study

primary endpoint based on published studies which found an association between post-transplant peak-AST and EAD, primary non-function, graft survival and patient survival. Serum AST was measured daily during the first post-transplant week, and the peak level was defined as the highest of these values (in IU/L). The COPE WP02 study was powered to detect a 33% reduction (to 401.67 IU/L) with 90% power at a 5% significance level, requiring 220 transplants (110 per arm).

1. Clinical Inclusion and Exclusion Criteria
   Randomization in the COPE clinical study was limited to livers that met the following inclusion criteria:

   Donor Inclusion Criteria
   Donors over the age of 16 years. Liver allografts from donation after brain death (DBD), standard and extended criteria donors (SCD, ECD) and donation after circulatory death (DCD) donors.

   Randomization of livers was not permitted in the COPE clinical study if they met any of the following exclusion criteria:

   Donor Exclusion Criteria
   Living donors; liver intended for split transplant; donor age <16 years; liver in which investigator is unwilling to randomize to either arm.

   Enrollment in the COPE clinical study was limited to subjects (recipients) that met the following inclusion criteria:

   Recipient Inclusion Criteria
   Adult patients (18 years or more), active on the waiting list for liver transplantation; able to give informed consent.

   Subjects were not permitted to enroll in the COPE clinical study if they met any of the following exclusion criteria:

   Recipient Exclusion Criteria
   Age less than 18 years; acute/fulminant liver failure; transplantation of more than one organ (e.g. liver and kidney); refusal of informed consent; unable to give informed consent.

2. Follow-up Schedule
   The study follow-up schedule included daily follow-up through Day 7, Day 10, Day 30, 6 Months, 12 Months and 24 Months.

3. Clinical Endpoints
   Primary Endpoints
   Difference in peak serum aspartate transaminase level (AST) within 7 days post-transplant between the two treatment arms. Serum AST will be measured daily during the first post-transplant week, and the peak level will be defined as the

highest of these values (in IU/L). In order to ensure consistency, the first post-transplant measurement should be taken at 12 to 24 hours post-reperfusion.

Secondary Endpoints

- Primary non-function: irreversible graft dysfunction requiring emergency liver replacement during the first 10 days after liver transplantation, in the absence of technical or immunological causes

- Graft survival at 30 days and 6, 12- and 24-months following transplantation

- Patient survival at 30 days and 6, 12- and 24-months following transplantation

- Daily serum bilirubin, GGT, AST and INR at days 1-7 following transplantation

- Daily serum lactate at Days 1-7 while admitted to ICU

- Serum bilirubin, GGT, AST and INR at day 30 and months 6, 12 and 24 following transplantation.

- EAD defined by any one of:
    - Bilirubin >170 μmol/L (10 mg/dL) on day 7 post-transplant
    - INR >1.6 on day 7 post-transplant.
    - Peak AST >2000 IU/L within the first 7 days post-transplant

- Post-reperfusion syndrome, defined as a decrease in mean arterial pressure (MAP) of more than 30% from the baseline value for more than one minute during the first five minutes after reperfusion

- Length of stay in high level (HDU/ITU) care

- Length of hospital stay

- Need for renal replacement therapy (RRT) (hemodialysis, hemofiltration, hemodiafiltration)

- Estimated Glomerular Filtration Rate (eGFR)

- Histological evidence of reperfusion injury in post-reperfusion biopsies (taken immediately prior to abdominal closure)

- Evidence of biliary strictures on magnetic resonance cholangiography (MRCP) at 6 months post-transplant

- Perfusion parameters (logged automatically by the device):
    - Arterial and caval pressures (in mmHg)

- Arterial, portal, and caval flow rates (in ml/min)
- pO_2, pCO_2,and pH
- Blood temperature (°C), glucose (mmol/L) and bile production (mL/h)
- Perfusate ALT and AST at 15 minutes, 1 hour, and the end of NMP
- Perfusate IL6, TNF, vWF at 15 minutes, 1 hour, and the end of NMP

- Organ discard rate

- Perfusate culture. At the end of preservation, a sample will be taken for microbiological culture (cold preservation or warm perfusate)

- Adverse event rates and severity, graded according to the Clavien-Dindo classification
  - Recipient infection
  - Biopsy proven acute rejection
  - Biliary complications (biliary strictures - anastomotic and non-anastomotic, bile duct leaks)
  - Vascular complications (bleeding, hepatic artery stenosis, hepatic artery thrombosis, portal vein thrombosis
  - Reoperation rate
  - Technical complications/device failures

- Limited data collected for health economic analysis utilizing:
  - Logistical costs measured using national unit costs where available.
  - Healthcare resource use; measured by a combination of hospital episode records and a patient-completed resource use log.
  - Quality of life by delivery of the EQ-5D-5L questionnaire at baseline, day 30 and month 6 post-transplant.

B. Accountability of COPE Trial Cohort

The trial enrolled subjects from seven centers between 26 June 2014 and 8 March 2016. The study has completed 2-year follow-up. In order for 220 transplanted livers to be included in the trial, 335 organ randomizations took place with 170 livers allocated to NMP and 164 allocated to the control arm (SCS). One randomization occurred in error before required approval was in place, therefore, this liver was excluded. Sixty-four livers (33 in the NMP and 31 in the SCS arm) were excluded after randomization and 50 livers (16 in the NMP and 32 in the SCS arm) discarded before transplantation, leaving 222 transplanted livers.

Figure 7 details donor randomization and subject enrollment in the NMP and SCS cohorts.

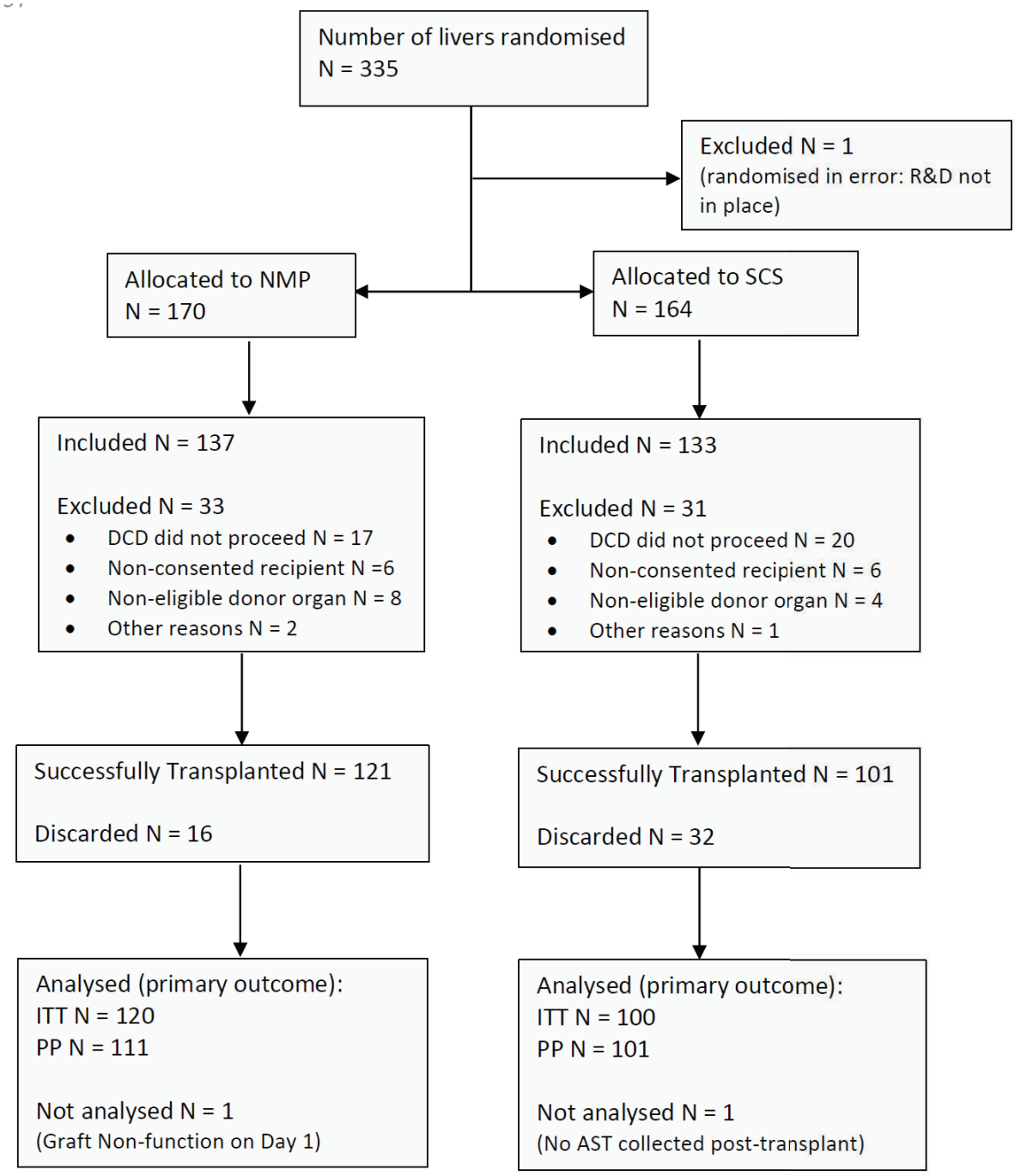

Figure 7: Subject Disposition Flow Chart of Enrollment and Analysis

Livers were excluded after randomization if they were later found to be ineligible for the trial. The possible reasons are listed in the table below.

Discarded livers are those that did not proceed to transplant due to the implanting surgeon's decision. These are reported below followed by the reasons for discards.

Table 27: Reason for Discarding or Declining Livers in COPE Trial

Reason	NMP	SCS	Total
Steatosis	13	24	37
Prolonged WIT	2	6	8
Poor perfusion parameters	5	0	5
Device user error	4	0	4
Donor problem (e.g. malignancy)	2	2	4
Abnormal lesion	0	3	3
Fibrosis	1	1	2
Poor in-situ perfusion	1	2	3
Capsular damange	1	1	2
Device error	1	0	1
Injury to hepatic artery	0	1	1
Parenchymal damage	1	0	1
Other	1	1	2

C. COPE Study Population Demographics and Baseline Parameters

Liver donors in both NMP and SCS were similar (**Table 28**). Overall, 36.8% of randomized liver donors were DCD (37.1% NMP, 36.6% SCS). The population was predominantly male (59.1% NMP, 57.1% SCS) and had a median age of 56 years old. The median UK-DRI was 1.5 overall (1.53 NMP, 1.49 SCS).

Recipient demographics are shown in **Table 29**. Overall, the study population was comprised of 72.1% males and had a median age of 55 years. There were no notable differences between the two cohorts with respect to age of recipients, proportion of males, BMI, or MELD score (**Table 29**). The NMP arm had a greater number of recipients receiving DCD livers (28.1% DCD in NMP arm versus 20.8% in SCS arm).

Table 28: Donor Characteristics

Stratification factors (all randomised livers)	NMP (N = 170)	SCS (N = 164)	Total (N = 334)
Donor type*			

DBD	107 (62.9%)	104 (63.4%)	211 (63.2%)
DCD	63 (37.1%)	60 (36.6%)	123 (36.8%)
Donor demographics (after exclusions)	NMP (N = 137)	SCS (N = 133)	Total (N = 270)
Gender*			
Female	54 (39.4%)	57 (42.9%)	111 (41.1%)
Male	81 (59.1%)	76 (57.1%)	157 (58.2%)
(missing)	2 (1.5%)	0 (0.0%)	2 (0.7%)
Age^	56 (45, 67) (16, 84)	56 (47, 66) (20, 86)	56 (46, 66) (16, 86)
Ethnicity*			
African-Caribbean	3 (2.2%)	1 (0.8%)	4 (1.5%)
Caucasian	131 (95.6%)	128 (96.2%)	259 (95.9%)
Other	1 (0.7%)	4 (3.0%)	5 (1.9%)
(missing)	2 (1.5%)	0 (0.0%)	2 (0.7%)
Cause of death			
CVA	74 (54.0%)	74 (55.6%)	148 (54.8%)
Hypoxia	30 (21.9%)	32 (24.1%)	62 (23.0%)
Trauma	17 (12.4%)	16 (12.0%)	33 (12.2%)
Other	14 (10.2%)	11 (8.3%)	25 (9.3%)
(missing)	2 (1.5%)	0 (0.0%)	2 (0.7%)
BMI^	26.26 (23.66, 30.52) (16.42, 46.65)	27.01 (23.74, 30.56) (17.24, 49.96)	26.51 (23.69, 30.54) (16.42, 49.96)
(missing)	2 (1.5%)	0 (0.0%)	2 (0.7%)
UK-Donor risk index^	1.53 (1.19, 2.63) (0.78, 6.35)	1.49 (1.22, 2.44) (0.77, 4.58)	1.50 (1.21, 2.49) (0.77, 6.35)
(missing)	41 (29.9%)	53 (39.8%)	94 (34.8%)
ET-Donor risk index^	1.72 (1.47, 2.09) (0.98, 4.31)	1.72 (1.50, 2.10) (1.06, 3.49)	1.72 (1.48, 2.10) (0.98, 4.31)
(missing)	16 (11.7%)	19 (14.3%)	35 (13.0%)

^Median, IQR and full range reported.
*Frequency and column percentages reported.

Table 29: Recipient Demographics

Recipient demographics *(transplanted livers)*	**NMP (N = 121)**	**SCS (N = 101)**	**Total (N = 222)**
Donor type*			

DBD	87 (71.9%)	80 (79.2 %)	167 (75.2%)
DCD	34 (28.1%)	21 (20.8%)	55 (24.8%)
Gender*			
Female	35 (28.9%)	27 (26.7%)	62 (27.9%)
Male	86 (71.1%)	74 (73.3%)	160 (72.1%)
Age^	55 (48, 62) (20, 72)	55 (48,62) (22, 70)	55 (48, 62) (20, 72)
Cause of Liver Failure*			
Alcoholic	36 (29.8%)	29 (28.7%)	65 (29.3%)
Auto-Immune Hepatitis	2 (1.7%)	5 (5.0%)	7 (3.2%)
Drug Induced	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hepatitis B	3 (2.5%)	2 (2.0%)	5 (2.3%)
Hepatitis C	4 (3.3%)	4 (4.0%)	8 (3.6%)
Hepatocellular Carcinoma on background of Cirrhosis	15 (12.4%)	16 (15.8%)	31 (14.0%)
Hepatocellular Carcinoma without Cirrhosis	4 (3.3%)	2 (2.0%)	6 (2.7%)
Metabolic	1 (0.8%)	0 (0.0%)	1 (0.5%)
Non-Alcoholic Fatty Liver Disease	2 (1.7%)	3 (3.0%)	5 (2.3%)
Non-Alcoholic Steato-Hepatitis	9 (7.4%)	8 (7.9%)	17 (7.7%)
Other Cancers	1 (0.8%)	0 (0.0%)	1 (0.5%)
Primary Biliary Cirrhosis	10 (8.3%)	3 (3.0%)	13 (5.9%)
Primary Sclerosis Cholangitis	18 (14.9%)	13 (12.9%)	31 (14.0%)
Other	16 (13.2%)	16 (15.8%)	32 (14.4%)
BMI^	26.18 (23.12, 32.39)	26.94 (24.36, 30.42)	26.47 (23.72, 31.64)
	(18.02, 50.99)	(18.91, 42.95)	(18.02, 50.99)
(missing)	0 (0.0%)	1 (1.0%)	1 (0.4%)
Retransplant*	12 (9.9%)	8 (7.9%)	20 (9.0%)
MELD score^	13 (10, 18) (6, 35)	14 (9, 18) (6, 29)	14 (10, 18) (6, 35)
UK-Donor risk index^	1.45 (1.17, 2.55)	1.43 (1.20, 2.19)	1.44 (1.19, 2.39)
	(0.78, 6.35)	(0.77, 3.42)	(0.77, 6.35)
(missing)	37 (30.6%)	34 (33.7%)	71 (32.0%)
ET-Donor risk index^	1.70 (1.47, 2.07)	1.71 (1.50, 2.01)	1.70 (1.48, 2.04)
	(0.98, 4.31)	(1.06 3.49)	(0.98, 4.31)
(missing)	13 (10.7%)	13 (12.9%)	26 (11.8%)

^Median, IQR and full range reported.

*Frequency and column percentages reported.

‡Transplant center refers to the recipient center were the liver was actually transplanted. In 4 UK livers

this differs from the centre reported in the stratification factors table.

Liver Transport and Preservation

Total preservation time was measured from the start of cold aortic perfusion in the donor until graft reperfusion in the recipient. The median total preservation time for the NMP group (n=121) and SCS group (n=101) was 714 minutes and 465 minutes, respectively. For the SCS arm, this preservation time was entirely cold ischemia time. The NMP arm had a median cold ischemia time of 126 minutes and median machine perfusion time of 547.5 minutes. Within the NMP arm, there was no significant difference in median perfusion time between DBD and DCD livers. The transplant procedures did not differ between groups with a median total operative time of 333 minutes and 345 minutes in the NMP and SCS arms, respectively.

There was a statistically significant higher organ discard rate after randomization in livers randomized to the SCS group versus the NMP group (**Table 30**). The observed organ discard rate in the SCS arm was 24.1% (32/133) versus 11.7% in the NMP group (16/137). This difference was statistically significant (-12.4% (95% C.I. - 21.4%, -3.3%); p=0.008).

Table 30: Discarded livers by treatment arm and discard rate

Discarded	NMP	SCS	Total
No	121 (88.3%)	101 (75.9%)	222 (82.2%)
Yes	16 (11.7%)	32 (24.1%)	48 (17.8%)
Total	137	133	270

Table 31: Reasons for discarding/declining livers

Reason	NMP	SCS	Total
Steatosis	13	24	37
Prolonged WIT	2	6	8
Poor Perfusion Parameters	5	0	5
Device Use Error	4	0	4
Donor Problem (eg, malignancy)	2	2	4
Abnormal Lesion	0	3	3
Fibrosis	1	1	2
Poor *in-situ* Perfusion	1	2	3

Capsular Damage	1	1	2
Device Error	1	0	1
Injury due to Hepatic Artery	0	1	1
Parenchymal Damage	1	0	1
Other	1	1	2

One NMP organ discard was the result of a device error (hepatic artery hypoperfusion due to pinch valve miscalibration) in an already marginal organ. Despite the overall lower discard rates in the NMP arm, the Agency notes that 4 organs were discarded or declined due to device use error, 1 due to device error, and 5 due to poor perfusion parameters (**Table 31**). These device-related incidences resulted in graft losses and should be considered when evaluating the use of the OrganOx *metra*® on donor grafts.

D. COPE Study Safety and Effectiveness Results

Primary Endpoint Analysis
The primary endpoint was defined as the difference between the two treatments arms in peak AST within 7 days post-transplant. The primary analysis was based upon intent-to-treat (ITT) and included all livers successfully transplanted by assigned randomized arm. There were in total 222 liver transplants, 101 in the SCS arm and 121 in the NMP arm; however, for the ITT analysis 2 livers (1 in each arm) were excluded due to no AST values being available post-transplant; therefore 100 and 120 liver transplants were analyzed respectively in the SCS and NMP groups.

The COPE study was powered to detect a 33% reduction in peak AST (to 401.67 IU/L) with 90% power at a 5% significance level, requiring 220 transplants (110 per arm).

The primary outcome of peak AST during the first 7 days post-transplant was reduced by 49.4% in the NMP group compared to SCS when adjusted by center and donor type (geometric mean ratio 0.506, 95% C.I. 0.388 to 0.659 p<0.001) as shown in the adjusted analysis ANOVA model (**Table 32**). Unadjusted analysis (Student's t-test) and sensitivity analysis undertaken in the per-protocol population confirmed these results.

Table 32: Primary Outcome Results from the Adjusted Analysis (ANOVA model)

	NMP	**SCS**	**Difference / Mean ratio^ [% reduction]**
Mean ln Peak AST (95% C.I)	6.191 (6.013, 6.368)	6.872 (6.678, 7.066)	-0.681 (-0.946, -0.417)
Geometric Mean Peak AST (95% C.I.)	488.142 (408.856, 582.804)	964.934 (794.471, 1171.972)	0.506 (0.388, 0.659) [49.4% (34.1%, 61.2%)]

^First cell in this column refers to the mean difference in natural logarithm Peak AST (variable used to run the analysis models). The second cell in this column refers to the geometric mean ratio of the Peak AST, used to look at the reduction in the original measurement.

The significant difference is confirmed in the unadjusted analysis from the t-test. The reduction in peak AST between the NMP and the SCS group was 50.2% (95% C.I. 35.1% to 61.9%, p<0.001)

There was a significant difference between groups only for the area under the curve (AUC) of the Bilirubin (p=0.022) and the AST (p<0.001), Data from the first 7 days.

Liver function was assessed by measurement of different biochemical tests in the first 7 days post- transplant. These were compared between treatment groups by means of (AUC) and their average value over Day 1-7 as shown in **Table 33.**

There was a significant difference between groups in favor of NMP for the AUC of the Bilirubin (p=0.022) and the AST (p<0.001), as shown from the table below. Median and IQR are reported as well as the values available in each group.

Table 33: Results for AUC of Biochemical Tests by Treatment Groups in the first 7 days post-transplant

Biochemical test (AUC)	NMP	SCS	p-value
Bilirubin N	12.72 (7.10, 25.15) 119	17.25 (9.25, 30.79) 101	0.022
AST N	854 (514.5, 1651) 112	1649 (801, 2961.5) 99	<0.001
GGT N	1615 (914.5, 2308) 93	1785 (1016, 2605.5) 81	0.260
INR N	7.3 (6.65, 8.02) 118	7.26 (6.66, 8.3) 100	0.604
Creatinine N	5.75 (3.94, 8.40) 119	6.44 (4.47, 9.9) 101	0.155
Median and interquartile range displayed for each treatment group			

Early Allograft Dysfunction
(EAD) defined as the presence of at least one of the following:

a. Bilirubin >170 μmol/L (10mg/dL) on day 7 post-transplant
b. INR >1.6 on Day 7 post-transplant.
c. Peak aspartate transaminase (AST) >2000 IU/L within the first 7 days post-transplant

EAD was assessed in 216 recipients and was 74% less likely to occur in the NMP (12/119) than the SCS (29/97) arm (odds ratio 0.263 (95% C.I. 0.126, 0.550); p < 0.001). **Table 34** provides analysis on EAD by treatment group.

Table 34: EAD by Treatment Group

EAD	NMP	SCS	Total
No	107 (89.9%)	68 (70.1%)	175 (81.0%)
Yes	12 (10.1%)	29 (29.9%)	41 (19.0%)
Total	119	97	216
Difference = -19.8% (95% C.I. -30.4%, -9.2%)			p-value = <0.001
Odds Ratio = 0.263 (95% C.I. 0.126, 0.550)			p-value = <0.001
EAD was defined as any one of: a. Bilirubin >170 µmol/l (10mg/dL) on day 7 post-transplant b. INR >1.6 on day 7 post-transplant. c. Peak aspartate transaminase (AST) >2000 IU/L within the first 7 days post-transplant			

Graft Survival

A comparison in graft and patient survival between NMP and SCS livers was assessed by comparing PNF rates 10 days following liver transplantation and graft and patient survival rates at 30 days, 6, 12 and 24 months following transplantation. This data presents the data available at the time of 2 year follow-up data lock (23rd November 2018). No statistically significant differences were observed between the treatment arms for graft survival over time up to 24 months. There were in total 15 graft failures. The graft survival at 6 months is 0.942 (95% C.I 0.881 to 0.972) in the NMP group and 0.917 (95% C.I 0.841 to 0.958) in the SCS group. Refer to **Figure 8.**

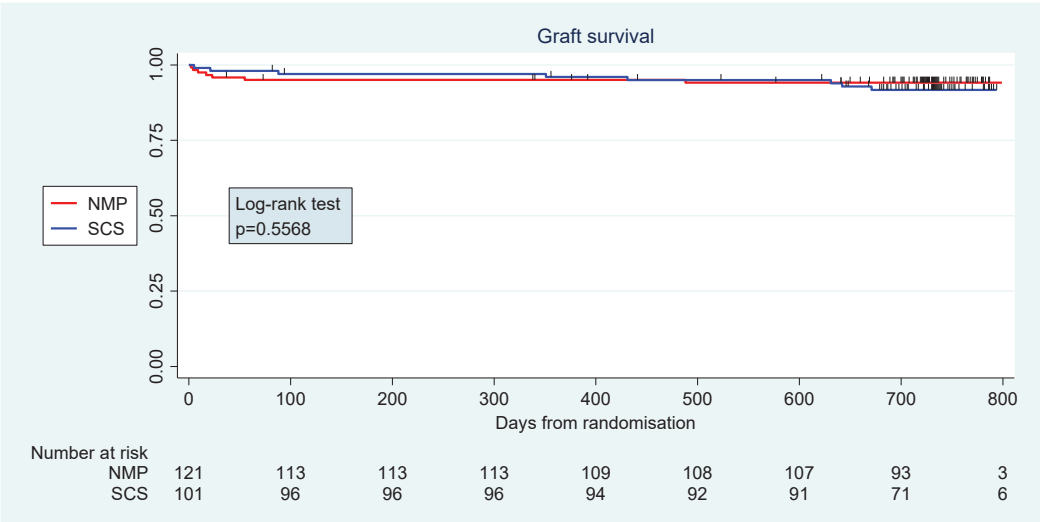

Figure 8: Kaplan-Meier for time to graft failure (ITT population)

Recipient Survival

Overall, 17 recipients died showing a survival of 0.932 (95% C.I 0.868 to 0.965) in the NMP group and 0.905 (95% C.I 0.824 to 0.950) in the SCS group. There were no statistically significant differences observed between the treatment arms for patient survival over time up to 24 months. Refer to **Figure 9**.

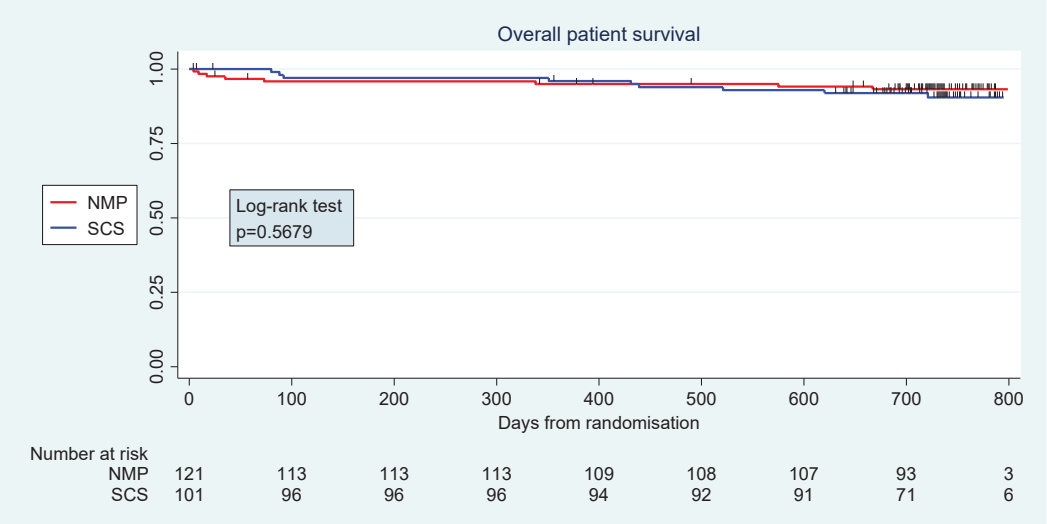

Figure 9: Death Kaplan-Meier (ITT Population)

Post-Reperfusion, Renal Replacement Therapy and Hospital Stay.

Post reperfusion syndrome was more common in the SCS group (33.0%) than in the NMP group (12.4%) and the difference (-20.6% (95% C.I. -31.6% to -9.6%)) is statistically significant (p <0.0001). Post reperfusion lactate levels were also significantly lower in the NMP group (p=0.018). There was no observed significant difference in the need for renal replacement therapy (RRT) or length of hospital or ICU-equivalentstay (HDU/ITU) between the two groups (**Table 35**).

Table 35: Post-Reperfusion, RRT and Hospital Stay Results

	NMP	SCS	Effect (95% C.I)*	p-value
Post reperfusion syndrome	15 (12.4%)	32 (33.0%)	-20.6% (-31.6%, -9.6%)	<0.001
Post reperfusion lactate‡	3.6 (2.6, 4.2)	4.1 (3.2, 5)		0.018
Need for RRT				
Day 1-7 post-transplant	26 (21.5%)	19 (18.8%)	2.7% (-7.9%, 13.2%)	0.621
Day 30	27 (22.3%)	20 (19.8%)	2.5 (-8.2%, 13.3%)	0.648
Month 6	27 (22.3%)	21 (20.8%)	1.5% (-9.3%, 12.4%)	0.784
Duration of RRT Day 1-7‡	4 (2, 6)	5 (4, 6)		0.346
Length of hospital stay‡	15 (10, 24)	15 (11, 24)		0.926
Length of HDU/ITU stay‡	4 (2, 7)	4 (3, 7)		0.339

*Effect reported is: geometric mean ratio [% reduction] for Peak AST; odds ratio for EAD; difference in proportions (%) for Post Reperfusion Syndrome and Need for RRT; not reported for outcomes where medians are reported and for survivals.

^Test not performed due to few events and no events in one arm.

‡Median and IQR reported, non-parametric test used.

Adverse effects that occurred in the COPE clinical study:

Adverse events were reported by the investigational sites and reviewed by two independent clinicians blinded to the treatment group (**Table 36**). All events were graded according to the Clavien-Dindo classification and any event graded IIIb or above was to be considered a SAE. The proportion of patients for whom adverse events were reported was similar in the two arms (55.4% NMP, 95% confidence interval 46.1–64.4% versus 57.4% SCS, 95% confidence interval, 47.2–67.2%) with a larger total number of events reported for SCS livers (128 NMP versus 164 SCS). A greater proportion of the SAEs (Clavien–Dindo grade ≥IIIb) were in the SCS arm (16.4% NMP versus 22% SCS), refer to **Table 37**. A full report of the adverse events by type is shown in **Table 38**.

Table 36: Clavien-Dindo Grading by Treatment Arm for all Adverse Events Reported

Clavien-Dindo Grading	NMP	SCS	Total
I	15 (11.7%)	30 (18.3%)	45 (15.4%)
II	64 (50.0%)	72 (43.9%)	136 (46.6%)
IIIa	28 (21.9%)	26 (15.9%)	54 (18.5%)
IIIb	8 (6.3%)	9 (5.5%)	17 (5.8%)
IVa	5 (3.9%)	15 (9.2%)	20 (6.9%)
IVb	3 (2.3%)	9 (5.5%)	12 (4.1%)
V	5 (3.9%)	3 (1.8%)	8 (2.7%)
Total	128	164	292

Table 37: Classification of Events by Seriousness (events not participants)

Classification	NMP	SCS	Total
AE	107 (83.6%)	128 (78.1%)	235 (80.5%)

SAE	21 (16.4%)	36 (22.0%)	57 (19.5%)
Total	128	164	292

Table 38: Adverse Events reported by type (events not participants)

Event Category	NMP	SCS	Total
Infection	25 (19.5%)	17 (10.4%)	42 (14.4%)
Chest	1	1	2
Blood	10	3	13
Biliary	6	0	6
Abdominal	2	3	5
Gastrointestinal	4	5	9
Other	2	5	7
Hepatic	44 (34.4%)	48 (29.3%)	92 (31.5%)
Bile leak	2	1	3
Biliary stricture (anastomotic)	9	11	20
Ischaemic cholangiopathy	1	3	4
Biliary other	1	0	1
Drainage of ascites	0	1	1
Hepatic artery aneurysm	0	1	1
Hepatic artery thrombosis	2	4	6
Hepatic artery stenosis	5	3	8
Hepatic artery other	0	2	2
Hepatic vein thrombosis	1	0	1
Portal vein thrombosis	2	0	2
Portal vein stenosis	2	0	2
Portal vein other	1	0	1
Graft dysfunction	3	2	5
Rejection	12	13	25

Other	3	7	10
Cardiovascular	5 (3.9%)	5 (3.1%)	10 (3.4%)
Congestive heart failure	1	0	1
Myocardial infarction	2	3	5
Other	2	2	4
Dermatologic	1 (0.8%)	0 (0.0%)	1 (0.3%)
Seroma	1	0	1
Gastrointestinal	5 (3.9%)	6 (3.7%)	11 (3.8%)
Colitis	0	1	1
Diarrhea	3	2	5
Other	2	3	5
Genitourinary	8 (6.3%)	17 (10.4%)	25 (8.6%)
Renal insufficiency	6	13	19
UTI	2	3	5
Other	0	1	1
Respiratory	4 (3.1%)	9 (5.5%)	13 (4.5%)
Cold/flu	0	1	1
Pneumonia	4	6	10
Shortness of breath	0	1	1
Other	0	1	1
Bleeding complications	9 (7.0%)	6 (3.7%)	15 (5.1%)
Bleeding – no transfusion required	0	2	2
Hemorrage (Bleeding requiring transfusion)	3	0	3
Bleeding from hepatic artery	1	1	2
Bleeding from liver parenchyma	2	0	2
Other	3	3	6
Fluid Collection	7 (5.5%)	18 (11.0%)	25 (8.6%)
Abdominal	5	10	15

Pleural	2	7	9
Other	0	1	1
Other systemic diseases	17 (13.3%)	38 (23.2%)	55 (18.8%)
Total	128	164	292

COPE WP02 Study Conclusion

The primary outcome of peak AST during the first 7 days post-transplant was reduced by 49.4% in the NMP group compared to SCS when adjusted by center and donor type (geometric mean ratio 0.506, 95% C.I. 0.388 to 0.659 p<0.001). Also, the odds of developing EAD in the NMP arm were 74% lower than the SCS arm. However, despite the observed reduction in both, peak AST during the first 7 days post-transplant and EAD rates in the NMP arm, there was no correlation with relevant clinical outcomes such as patient and graft survival, ICU-equivalent and hospital stay.

No statistically significant differences were observed between the treatment arms for graft and patient survival over time up to 24 months. The length of hospital stay and ICU-equivalent stay were comparable across arms.

There was no significant difference in the need for renal replacement therapy between the two groups.

Mean preservation time was 54% longer in the NMP arm (11hrs and 54 min) compared to SCS (7 hrs and 45 min; p< 0.001) with lower EAD rates and comparable patient and graf survival. This is a clinically relevant advantage; however, these finding were not corroborated in the US trial.

There was an overall lower discard rate in the NMP arm (12%) compared to the SCS arm (24%). However, FDA noted organs discarded or declined due to device use (such as device user error, device error, or poor perfusion parameters; see **Table 30**). These device-related incidences resulted in graft losses and should be considered when weighing the potential advantages of the OrganOx *metra*® over standard cold storage.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Gastroenterology and Urology Device Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The evidence demonstrates that OrganOx *metra*® effectively transports and sustains donor livers destined for transplantation in a functioning state for periods up to 12 hours. In a population of higher risk, but acceptable per standard of care liver grafts, OrganOx evaluated the *metra*® in two randomized, controlled trials (US IDE Trial & COPE WP02). These trials demonstrated results consistent with *metra*®'s ability to reduce preservation injury and graft dysfunction, as measured by markers of early post-transplant allograft function, including EAD and peak AST.

The US IDE Study enrolled livers that would typically have been transplanted using SCS per usual US transplant practice. Risk factors for EAD, such as donor age, BMI, and degree of steatosis did not differ significantly between groups. Cold ischemia time is a significant risk factor for EAD and it is notable that in the SCS arm of this study it was shorter (302.50 minutes) than the expected US average, which has been reported as approximately 5.5 hours (330 minutes) for a similar population.[1] The overall donor risk index was equivalent between the two groups, with values on the high side of the risk spectrum (NMP mean 1.63 ± 0.32 versus SCS mean 1.62 ± 0.33). For perspective on how this risk reflects real-world conditions, Feng et al. reported a 7.7% survival difference at 1 year for grafts with a donor risk index ≤1.0 compared to grafts with a risk index between 1.5 and 1.6.[7]

In the US IDE Study, the As-Treated analysis resulted in EAD rates of 18.7% (95% CI: 12.8%, 26.5%) NMP versus 24.9% SCS (95% CI: 18.2%, 33.1%; superiority p-value = 0.115). EAD rates in the ITT NMP population were 20.6% (95% CI: 14.5%, 28.5%) versus 23.7% in the SCS arm (95% CIT: 17.1%, 31.9%; superiority p-value = 0.275). Olthoff et al. (2010), who developed the EAD definition, reported an EAD incidence of 23%, based on data from approximately 300 liver transplants from a broad spectrum of low to high risk grafts preserved by SCS from 3 US centers between 2004 and 2005.[1] Estimates of EAD rates in DCD donors have been shown to be closer to 40%.[8] The overall rate of EAD in the US SCS arm (24.9%) was close to the Olthoff et al finding; however the US IDE Study enrolled a population of livers that are higher than typical risk of EAD per the DRI measure. In subjects with DCD liver transplants for the As-Treated analysis, there is a trend towards a device effect (22.8% NMP versus 44.6% SCS); however, the study was not powered to measure the significance of this effect in DCD subjects only. Upon the early observation in this study that a learning curve existed for optimal cannulation technique, OrganOx provided enhanced training at all sites. After this point in time, the occurrence of EAD in the NMP arm was reduced. However, the sample size of this cohort was underpowered to assess such a difference in outcomes.

The COPE WP02 study also enrolled livers that would typically have been transplanted using SCS per European transplant practice: whole livers from DBD and DCD (Maastricht category III) donors. The primary endpoint was defined as the difference between the two treatment arms in the peak AST within 7 days post-transplant. EAD was also reported.

The primary outcome of peak AST during the first 7 days post-transplant was reduced by 49.4% in the NMP group compared to SCS when adjusted by center and donor type (geometric mean ratio 0.506, 95% C.I. 0.388 to 0.659 p<0.001). The clinical significance of this finding is unclear. EAD was also reported and consistent with this result, EAD was reported in 10.1% of subjects in the NMP arm compared to 29.9% of subjects in the SCS arm. Compared to the US IDE Study, cold ischemia times in the COPE WP02 study in the SCS arm (median 465 minutes) were substantially longer than experienced in the US IDE study (median 302.5 minutes), and perhaps as a result lower levels of peak AST were seen in the SCS arm of the US IDE compared to the COPE WP02 study (964.94 COPE WP02; 722.41 US IDE).

Both studies compared to a contemporaneous, randomized cohort of livers preserved with SCS. With respect to prevention of preservation injury and graft dysfunction, OrganOx *metra*® demonstrated effectiveness comparable to that of livers stored by static cold storage. Although the US IDE Study did not meet the superiority hypothesis, comparative outcomes to SCS demonstrate a benefit in liver preservation similar to the current standard of care.

In both studies, there was no clinically meaningful difference between graft and patient survival, as they were not powered to show such differences. However, the studies both demonstrate improvements in secondary outcomes related to NMP. Occurrence of post reperfusion syndrome was more common in the SCS arms than in the NMP arms in both trials. In the US IDEstudy, 14.6% of subjects in the SCS arm experienced post-reperfusion syndrome compared to 5.9% in the NMP arm. In COPE WP02, the trend is the same (33.0% SCS versuss 12.4% NMP).

In support of the organ utilization benefit, the COPE WP02 study also demonstrated increased organ utilization in the NMP arm. The observed organ discard rate in the SCS arm was 24.1% (32/133) versus 11.7% in the NMP group (16/137), which was statistically significant (p=0.008). While it is unclear how the use of the NMP device contributed to this outcome, this finding was still favorable for the NMP device despite additional organs discarded due to device user error, device error, and poor perfusion. However, in both COPE WP02 and the US IDE Study, the full effect of NMP on utilization could not be assessed as livers recruited to these studies had to be suitable for either method of preservation.

B. <u>Safety Conclusions</u>

The risks of the device are based on nonclinical laboratory and animal studies as well as collected in clinical studies conducted to support PMA approval as described above.

The clinical evidence demonstrates that the OrganOx *metra*® is safe when used to transport and sustain donor livers destined for transplantation in a functioning state for periods up to 12 hours. The US IDE Study was conducted with safety oversight. There were no differences in safety profile between NMP and SCS arms that can be categorized as device-specific risks. The rates of deaths, graft failure, and SAEs were comparable between arms through both the 30 day and 12-month periods. There were no device-related deaths per the CEC adjudication.

Safety evaluations in the COPE WP02 study showed results consistent with the US IDE Study. Incidence of all AEs and SAEs (defined with Clavien-Dindo grade ≥ 3b) were numerically higher in the SCS arm. The rates of deaths and graft failure through 24 months were comparable between arms.

C. **Benefit-Risk Determination**

The probable benefits of the device are based on data collected in clinical studies conducted to support PMA approval as described above. While the US WP01 study did not meet its primary endpoint of superiority of the NMP arm relative to the SCS arm with respect to EAD, the rates of EAD were comparable across arms, particularly after introduction of the enhanced training during the WP01 study.Additionally, graft survival, rates of ischemia-reperfusion injury, organ utilization, and post-transplant recipient ICU and hospital stay length were comparable between the SCS and NMP arms. The rates of post-reperfusion syndrome were numerically lower in the NMP cohort than in the SCS cohort; this effect was more pronounced in the DBD-NMP subgroup without showing any clinical benefits. Biliary complications between Day 7 and Month 6 post-transplant were numerically lower in the NMP arm than the SCS arm; effects were more pronounced in the DCD-NMP cohort, particularly after the enhanced training introduced during the study. Finally, the US WP01 study demonstrated that livers preserved via NMP using the OrganOx *metra*® device demonstrated lower rates of median AST (Days 1-7 post-transplant) and peak AST; median ALT (Days 1-7 post-transplant) and peak AST; and median creatine (Days 1-7 post-transplant) than livers preserved using SCS; all other measures of biochemical liver function were comparable across arms. The available clinical data demonstrates that livers preserved via NMP using the OrganOx *metra*® device have comparable outcomes to those preserved via SCS, with additional benefits with respect to improved post-perfusion syndrome rates, reduced rates of biliary complications after enhanced training (except for anastomotic complications), and lower levels of AST, ALT, and creatinine levels as compared to SCS-preserved liver grafts. This conclusion is generally supported by similar data from the UK WP02 trial. Differences in EAD outcomes might be due to differences in CIT and subject criteria.

The risks of the device are also based on data collected in a clinical studies conducted to support PMA approval as described above. Risks associated with device use include device malfunction, improper device use, and operator mishandling of donor grafts. Device malfunction or misuse could result in poor donor graft quality, emergency preservation of the donor graft through alternative means (such as SCS), a more complicated transplantation procedure, or loss of the donor graft. In the US WP01 study, two organs were discarded following NMP due to “inadequate NMP” during transport, possibly due to user error. However, in the WP02 study, the overall rate of organ discard due to any reason was lower in the NMP arm. Additionally, the US clinical study revealed higher rates of anatomatic biliary complications in the NMP arm, which may have been caused in part due to improper bile duct cannulation. Finally, while overall rates of cholangitis and ischemic cholangiopathy were low across arms, the incidence of both were higher in NMP relative to SCS. Many of the adverse events reported in the WP01 study are typical for liver transplantation. Adverse events and risks that could be reasonably attributed to device use have been mitigated via non-clinical and clinical

evaluations and the ability of the OrganOx *metra*® device to rapidly default to SCS preservation in the event of a device malfunction. OrganOxintroduced enhanced trainings for *metra*® operators to reduce the risk of device misuse or donor graft mishandling. Additional device-related risks are further mitigated by the availability of OrganOx-sponsored training and technical support.

Additional factors to be considered in determining the risks and benefits of the OrganOx *metra*® device include the effect of the enhanced training on clinical outcomes and the potential benefits of the device with respect to DCD donor grafts. In the US WP01 Study, the applicant initiated Enhanced Training due to higher rates of EAD in the NMP group with a focus on cannulation technique. The rates of EAD in the NMP armseemingly improved after the training, but because this training was introduced during the study, it is not entirely clear if the improved EAD outcomes were due to the training or external factors. The post-training improvements have factored into the Agency's benefit-risk determination for this device, but definitive conclusions about the benefit of enhanced training on clinical outcomes should be investigated in a prospective, controlled manner in the future. Additionally, the clinical data suggests possible improved outcomes in higher risk donor organs (such as DCD donor livers) with the caveat that these improvements were evaluated via *post-hoc* analyses. This preliminary data is promising should also be fully explored in a controlled manner. Both considerations will be addressed via Post-Approval studies to be conducted as Conditions of Approval of this PMA.

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that the OrganOx *metra*® system in transporting and sustaining livers destined for transplantation in a functioning state for periods up to 12 hours, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The evidence demonstrates that the OrganOx *metra*® effectively transports and sustains donor livers destined for transplantation in a functioning state via normothermic machine perfusion for periods up to 12 hours. With respect to prevention of preservation injury and graft dysfunction, OrganOx *metra*® demonstrated effectiveness comparable to that of livers stored by static cold storage.

The available clinical data demonstrates that livers preserved via normothermic machine perfusion using the OrganOx *metra*® device have comparable outcomes to those preserved via static cold storage, with additional benefits with respect to improved post-perfusion syndrome rates, reduced rates of biliary complications after enhanced training (except for anastomotic complications), and lower levels of AST, ALT, and creatinine levels as compared to SCS-preserved liver grafts. This conclusion is generally supported by similar data from the UK WP02 trial.

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

XIV. CDRH DECISION

CDRH issued an approval order on 12/9/2021. The final clinical conditions of approval cited in the approval order are described below.

1. OrganOx *metra*® WP01 Long-Term Follow-Up PAS (Protocol Version 1, dated November 2021)

The WP01 Long-Term Follow-Up PAS is an observational study designed to evaluate the long-term outcomes of patients from the WP01 trial. The outcomes of up to 136 of the 136 patients randomized into the normothermic machine perfusion (NMP) cohort, and up to 129 of the 130 patients randomized into the static cold storage (SCS) cohort will be monitored through 36 months post-transplant.

This study has two primary objectives: the first is to assess the graft and subject survival in the identified subjects. Graft and subject survival rates will be evaluated using 24-month and 36-month data as reported in the United Network of Organ Sharing (UNOS) database. The second primary objective is to assess evidence of biliary complications in identified subjects. This objective will be evaluated using biochemical (bilirubin) and clinical (cause of graft failure and subject death) outcomes as reported in UNOS.

This study has two secondary objectives: The first is to report post-transplant malignancy in identified subjects. This objective will be evaluated using post-transplant malignancy information as reported in UNOS. The second secondary endpoint is to report viral detection in identified subjects. This objective will be evaluated using UNOS data.

You must meet the following timelines for the WP01 Long-Term Follow-Up PAS:

- Submit an annual report by February 28 of each year, beginning on February 28, 2022
- Submit an interim report by August 31, 2022 and August 31, 2023
- Complete 36-month follow-up on all PAS participants by February 28, 2023
- Submit a Final Report by May 31, 2023

2. OrganOx *metra*® WP02 Continued Access Protocol Long-Term Follow-Up PAS (Protocol Version 1, dated November 2021)

The WP02 CAP Long-Term Follow-Up PAS is an observational study designed to evaluate the long-term outcomes of patients from the WP02 trial. The outcomes of up to 105 of the 105 patients transplanted with NMP-perfused donor livers will be monitored through 36 months post-transplant.

This study has two primary objectives: the first is to assess graft and subject survival in the identified subjects. Graft and subject survival rates will be evaluated using 24-month and 36-month survival data as reported in the UNOS database. The second primary objective is to assess evidence of biliary complications in identified subjects. This objective will be evaluated using biochemical (bilirubin) and clinical (cause of graft failure and subject death) outcomes as reported in UNOS.

This study has two secondary objectives: The first is to report post-transplant malignancy in identified subjects. This objective will be evaluated using post-transplant malignancy information as reported in UNOS. The second secondary endpoint is to report viral detection in identified subjects. This objective will be evaluated using UNOS data.

You must meet the following timelines for the WP02 Continued Access Protocol Long-Term Follow-Up PAS:

- Submit an annual report by June 30 of each year, beginning on June 30, 2023
- Submit an interim report by December 31, 2023 and December 31, 2024
- Complete 36-month follow-up on all PAS participants by June 30, 2025
- Submit a Final Report by September 30, 2025

3. OrganOx *metra*® New Enrollment PAS (Protocol Version 1, dated November 2021)

The OrganOx *metra*® New Enrollment PAS is a multi-center, single-arm, unblinded post-approval study designed to compare recipients of PAS NMP livers versus IDE SCS livers with respect to adverse biliary-related events. Recruitment will take place at a minimum of 10 sites, which are UNOS member liver transplant centers.

The New Enrollment PAS study will include 210 transplanted livers from deceased DBD and DCD donors with a minimum of 40 transplanted livers from DCD donors. Enrolled subjects will be followed for 12 months post-transplant.

The primary objective is to compare the effect of NMP to SCS in the prevention of adverse biliary-related events as measured by biliary complications at 3-months, 6-months, and 12-months post-transplant.

There are two secondary objectives. The first is to assess graft survival rates at 3-months, 6-months, and 12-months post-transplant. The second secondary objective is to assess patient survival rates at 3-months, 6-months, and 12-months post-transplant.

In addition to the above data, the following preservation parameters will be collected for all study livers: degree of steatosis at time of retrieval; quality of *in-situ* perfusion; perfusion parameters for NMP livers; perfusate ALT and AST (for NMP livers); lactate levels (for NMP livers); perfusion solution used for in situ and back-bench perfusion; perfusion solution used for organ transport (SCS organs only); and glucose levels.

The following inpatient/discharge assessment data will be evaluated: length of stay in ICU; total length of hospital stay; primary-non function via evaluation of irreversible

graft dysfunction requiring emergency liver replacement during the first 10 days after liver transplantation; biliary complications; biliary interventions; graft and subject survival; device-related adverse events.

A modified intent-to-treat (mITT) analysis will be performed for all outcomes as the primary analysis. The New Enrollment NMP cohort in the mITT population will be compared against the as-treated IDE control population (SCS) for the primary outcome. The primary outcome, the difference in biliary complication rates, will be analyzed using propensity score stratification to adjust for potential differences in risk factors. Propensity modeling will be performed based on the baseline characteristics of sex, donor age, recipient age, donor type, and recipient MELD score.

Subgroup analyses will be performed for donor type (DCD versus DBD), by donor risk index (DRI), and by duration of machine preservation in the NMP arm of the study.

In the event of missing data, the extent and types of missing data for key study variables will be assessed as part of sensitivity analyses and reported upon. Withdrawals from the study after transplantation will be documented and a summary of withdrawals will be performed. For all study endpoints, data will be summarized for those recipients with available data.

You must meet the following timelines for the New Enrollment PAS:

a. The first subject is enrolled within 6 months of the study protocol approval date
b. 20% of subjects are enrolled within 12 months of the study protocol approval date
c. 50% of subject are enrolled within 18 months of the study protocol approval date
d. 100% of subject are enrolled within 24 months of the study protocol approval date
e. The submission of final study report is due 3 months from study completion (i.e., last subject, last follow-up date)

The applicant's manufacturing facilities have been found to be in compliance with the Device Quality System (QS) regulation (21 CFR 820), via the supporting documentation provided in P200035, and through a risk-based assessment.

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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