SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Portable Ex-Vivo Organ Perfusion System for Donor Lung Preservation
Device Trade Name:	Organ Care System (OCS™) Lung System
Device Procode: QBA	
Applicant's Name and Address:	TransMedics Inc. 200 Minuteman Road, Suite 302 Andover, MA 01810
Date of Panel Recommendation:	May 17, 2017
Premarket Approval Application (PMA) Number:	P160013
Date of FDA Notice of Approval:	March 22, 2018
Priority Review:	Granted priority review status on May 23, 2016

II. INDICATION FOR USE

The TransMedics® Organ Care System (OCS™) Lung System is a portable organ perfusion, ventilation, and monitoring medical device indicated for the preservation of standard criteria donor lungs in a near physiologic, ventilated, and perfused state for double lung transplantation.

III. CONTRAINDICATIONS

Moderate to severe traumatic donor lung injury with air leak (as seen on radiological studies, bronchial examination or final visual assessment in donor's chest) to avoid:

- Perfusate leakage from injury site into the airways and potential edema formation
- Inability to recruit donor lungs due to air leak

IV. WARNINGS AND PRECAUTIONS

WARNING— Only trained users are allowed to use the OCS™ Lung System.

WARNING—Safety and effectiveness of the OCS™ Lung System for marginal/extended criteria lungs, including donor lungs subjected to extended preservation times, have not been studied in the INSPIRE trial.

PRECAUTIONS— The safety and effectiveness of the OCS™ Lung System has not been studied in recipients with the following:

- Single Lung transplant
- Prior solid organ or bone marrow transplant
- Multi-organ transplants
- Chronic use of hemodialysis or diagnosis of chronic renal failure requiring dialysis

Safety and effectiveness of the OCS™ Lung System has not been studied for donor organs with Hepatitis B and Hepatitis C.

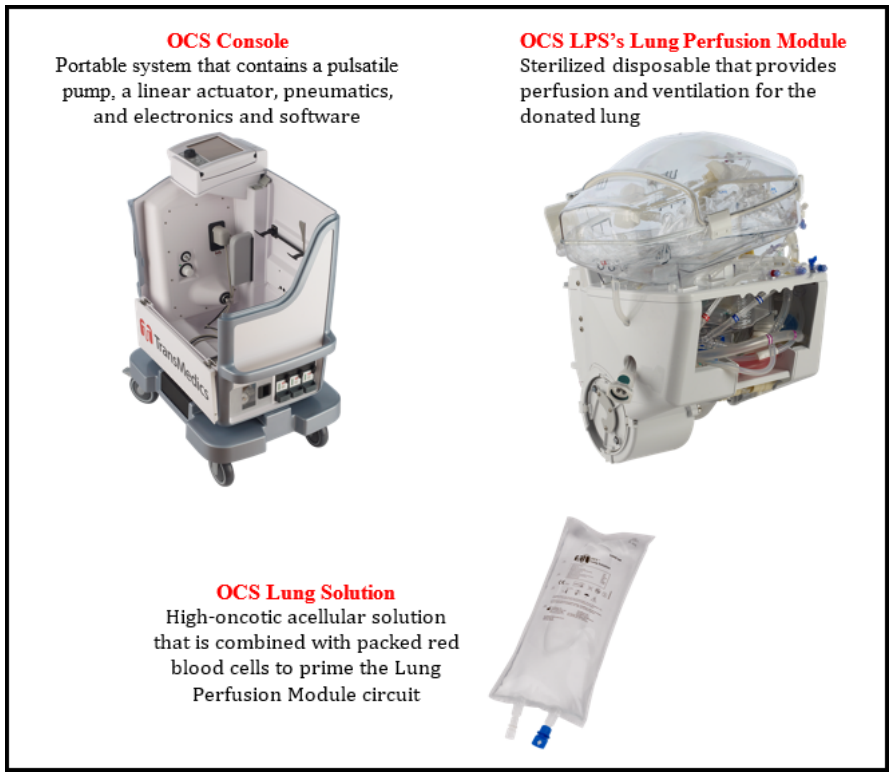
A device malfunction or user error could lead to a potential loss of a donor organ.

V. DEVICE DESCRIPTION

The **TransMedics® OCS™ Lung System** consists of the following major components:

- **Lung Console:** The Lung Console is a non-sterile, reusable, portable enclosure that houses an electronic display and non-sterile mechanical and electrical elements required to warm, pump, ventilate, and manage gas content of the perfusate.
- **Lung Perfusion Set (LPS)**: The Lung Perfusion Set includes a sterile, single-use perfusion module (Lung Perfusion Module or LPM) and various accessories. The perfusion module consists of an organ chamber and a circulatory system to perfuse and ventilate the lung. The supplied accessories connect the lung to the organ chamber and facilitate the management of fluids within the perfusion module.
- **OCS™ Lung Solution:** This is the high oncotic solution used for ex-vivo flush and perfusion of donor lungs when combined with packed red blood cells (pRBCs).

Figure 1: Major Components of OCS™ Lung System



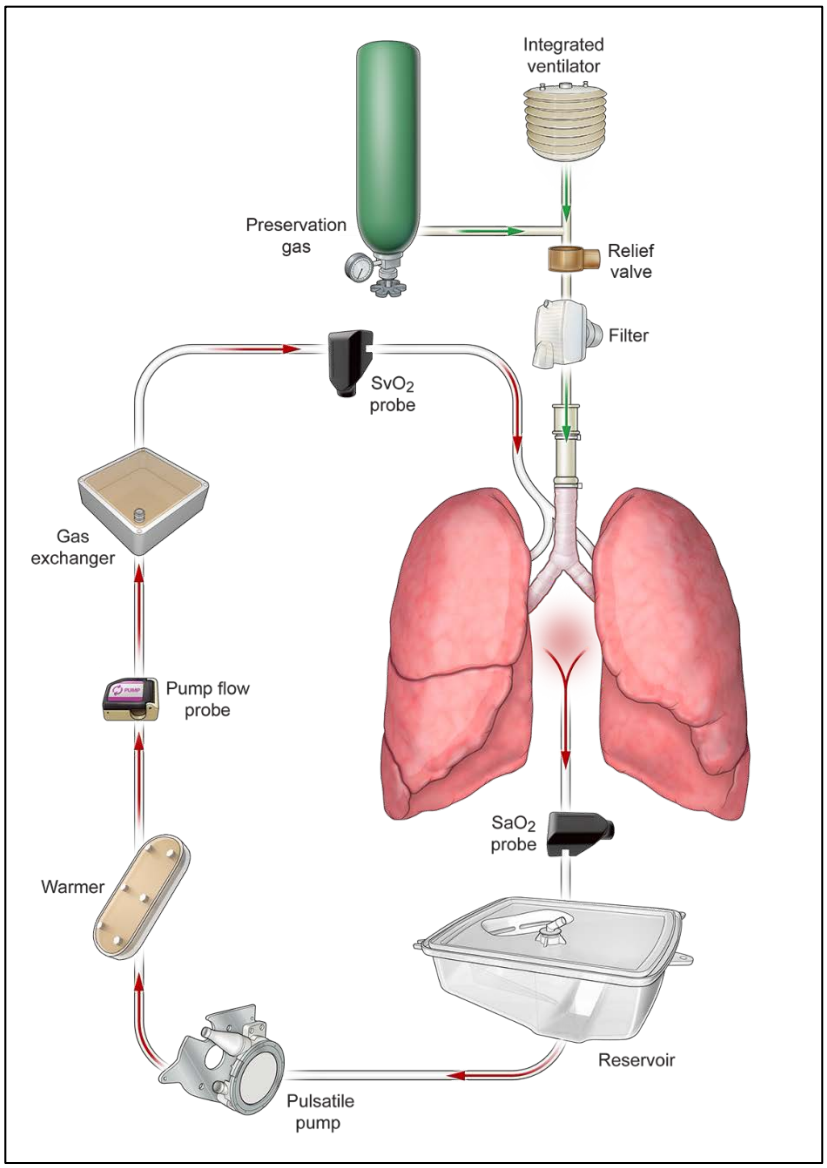
The OCS™ Lung System performs two primary functions to achieve its intended use:

1. **Perfusion and Ventilation**

   The OCS™ Lung System preserves ventilated lungs using warm oxygenated cellular perfusate. The system supports several ventilator modes to ensure both preservation and assessment of lung function during retrieval. Ventilator modes of the lung system include the following: Pause Preservation; Preservation; Continuous Monitoring; Bronchoscope Monitoring; and OFF Mode.

Figure 2 shows an overview of the circulation and ventilation.

Figure 2: Conceptual Diagram of the OCS™ Lung System



2. **Monitoring Capabilities**

The OCS™ Lung System was designed to provide a means to allow the transplantation team to evaluate the preservation conditions and the function of the organ during transport. The OCS™ Lung System incorporates a number of sensors to assess organ function and the preservation conditions during

transportation. Specifically, it monitors lung perfusion flow rates, airway pressure, vascular resistance, temperature, arterial and venous oxygen saturation, and HCT levels.

Please refer to the Clinical User Guide for additional details.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The conventional method for preservation of donor lungs is cold, static storage in a preservation solution prior to transplantation.

VII. MARKETING HISTORY

TransMedics has not marketed the OCS™ Lung System in the United States. In December 2011, TransMedics began distribution of the OCS™ Lung System in the European Union under CE-mark authorization. The OCS™ Lung System is classified as a Class IIa device under the European Medical Device Directive 93/42/EEC. In addition, the OCS™ Lung System is commercially available and marketed in Australia. The OCS™ Lung System has not been withdrawn from marketing for any reason related to the safety and effectiveness of this system.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events that were observed in subjects treated with the OCS™ Lung System in the INSPIRE clinical trial included: respiratory failure; pleural effusion; pneumothorax; hemothorax; bronchostenosis; pulmonary embolism; bronchial secretion retention; chylothorax; acute respiratory failure; diaphragmatic paralysis; emphysema; pulmonary edema; pneumonia; lung infection; bronchopneumonia; infection; bronchitis; lung infection pseudomonal; respiratory tract infection; diverticulitis; aspergillosis; fungaemia; parainfluenzae virus infection; postoperative wound infection; pseudomonas infection; toxoplasmosis; atrial fibrillation; cardiac arrest; cardiac failure congestive; tachycardia; myocardial ischaemia; pericarditis; right ventricular failure; ventricular fibrillation; acute renal failure; renal failure; hemorrhage; deep vein thrombosis; ischaemia; haemodynamic instability; orthostatic hypotension; shock; post-procedural hemorrhage; wound dehiscence; complications of transplant surgery; procedural complication; drug toxicity; weaning failure; wound complication; impaired gastric emptying; dysphagia; gastrointestinal hemorrhage; large intestine perforations; diarrhea; duodenal perforation; gastric ulcers; gastritis; gastrointestinal disorder; gastrointestinal ulcer hemorrhage; nausea; pancreatitis; lung transplant rejection; cerebrovascular accident; encephalopathy; brain edema; convulsion; cerebellar ischaemia; cerebral infarction; hypoxic encephalopathy; chest pain; impaired healing; leukopenia; coagulopathy; hyponatremia; myopathy; rhabdomyolysis; mechanical ventilation; transfusion; pyloric stenosis; antibiotic resistant staphylococcus test positive; angioedema.
Potential adverse events that may occur but were not observed in the INSPIRE Trial include: anemia; cough; gastroesophageal reflux disease; malignancy (post-transplant

lymph proliferative disorder (PTLD)); mucus plug; neurological dysfunction; pleural bleeding; and pulmonary infarction.

The rates of adverse events observed in subjects treated with the OCS Lung System and those treated with the standard of care cold storage were overall similar. For additional information, please see Part H of Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

TransMedics conducted the following nonclinical studies to evaluate the the OCS Lung System: (A) engineering bench testing; (B) biocompatibility; (C) software verification and validation; (D) electrical safety and EMC; (E) sterilization and shelf life; and (F) animal studies.

A. Engineering Bench Testing

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

B. Biocompatibility

TransMedics performed a series of biocompatibility studies to demonstrate the safety of the materials of the TransMedics LPS, which consists of the LPM and LPS Accessories. All studies were conducted in compliance with 21 CFR Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies (GLPs).

The LPS has been categorized for its body contact and duration of contact according to ISO 10993-1, Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing, to select the appropriate biocompatibility testing program. Biocompatibility tests and results are provided in Table 1 below.

Table 1: Biocompatibility Testing Summary for LPS

Biocompatibility Test	Results
Cytotoxicity Test	Non-cytotoxic
Sensitization (2 extracts)	No delayed dermal contact sensitization
Intracutaneous Reactivity (2 extracts)	No irritation
Acute Systemic Toxicity (2 extracts)	No systemic toxicity observed
Pyrogenicity – Material Mediated	Non-pyrogenic

Biocompatibility Test	Results
Pyrogenicity – Bacterial Endotoxin	Non-pyrogenic
In Vitro Hemolysis	Non-hemolytic
Genotoxicity – Bacterial Reverse Mutagen Study (2 extracts)	Non-mutagenic
Genotoxicity – Mouse Lymphoma Assay (2 extracts)	Non-mutagenic
Genotoxicity – Mouse Peripheral Blood Micronucleus (2 extracts)	Non-mutagenic
USP Physicochemical Tests • Non-volatile residue • Residue on Ignition • Heavy Metals • Buffering Capacity	Meets USP limits; no significant extractables

Additional biocompatibility testing was performed on the OCS™ Lung Solution including the OCS™ Lung Solution bag. The testing and results are summarized in Table 2 below.

Table 2: Biocompatibility Testing of OCS™ Lung Solution and Bag

Biocompatibility Test	Results
Cytotoxicity Test	Non-cytotoxic
Sensitization	No delayed dermal contact sensitization
Intracutaneous Reactivity	No irritation
Acute Systemic Toxicity	No systemic toxicity observed
Pyrogenicity – Material Mediated	Non-pyrogenic
Pyrogenicity – Bacterial Endotoxin	Non-pyrogenic
In Vitro Hemolysis	Non-hemolytic

C. Software Verification and Validation

TransMedics performed system level software verification and validation testing to demonstrate the OCS™ Lung System performs as intended. The device passed all testing and met its requirements. Software documentation has been provided in

accordance with the FDA guidance document entitled "Guidance for the Contents of Premarket Submissions for Software Contained in Medical Devices," dated May 11, 2005.

D. Electrical Safety and Electromagnetic Compatibility (EMC)

1. Electrical and Medical Device Safety

The OCS™ Lung System was tested to demonstrate that it meets the requirements for electrical safety according to Edition 3.1 of the IEC 60601-1 standard, as well as the ANSI/AMMI and CSA versions of the standard. Results are shown in Table 3 below.

Table 3: Summary of the Test Results for Electrical, Thermal, and Mechanical Safety

Test Description	IEC 60601-1 Clause	Result
General Requirements	4	Pass
General Requirements for Testing ME Equipment	5	Pass
Classification of ME Equipment and ME Systems	6	Pass
ME Equipment, Identification Marking and Documents	7	Pass
Protection Against Electrical Hazards from ME Equipment	8	Pass
Protection Against Mechanical Hazards of ME Equipment and ME Systems	9	Pass
Protection Against Unwanted and Excessive Radiation Hazards	10	N/A
Protection Against Excessive Temperatures and Other Hazards	11	Pass
Accuracy of Controls and Instruments and Protection Against Hazardous Outputs	12	Pass
Hazardous Situations and Fault Conditions	13	Pass
Programmable Medical Electrical Systems (PEMS)	14	Pass
Construction of ME Equipment	15	Pass
ME Systems	16	N/A

2. Electromagnetic Compatibility

The OCS™ Lung System was tested to demonstrate that it meets the electromagnetic compatibility requirements according to IEC 60601-1-2 (4th edition). Results are shown in Table 4 below.

Table 4: Summary of the Emission and Immunity Testing for OCS™ Lung System

Test	Standard	Test Level	Results
Radiated Emissions	CISPR 11	Group 1, Class A	Pass
AC Mains Conducted Emissions	CISPR 11	Group 1, Class A	Pass
Harmonics Emissions	IEC 61000-3-2	Class A	Pass
Voltage Fluctuation/ Flicker	IEC 61000-3-3	D_{MAX} = 4%	Pass
Electrostatic Discharge Immunity	IEC 61000-4-2	±8 kV Contact ±15 kV Air	Pass
Radiated RF Immunity	IEC 61000-4-3	3 V/m	Pass
Electrical Fast Transients Immunity	IEC 61000-4-4	±0.5 kV, ±1 kV, ±2 kV	Pass
Surge Immunity	IEC 61000-4-5	±0.5 kV, ±1 kV, Line-to-line ±0.5 kV, ±1 kV, ±2 kV, Line-to-PE	Pass
Conducted RF Immunity	IEC 61000-4-6	3 V_{RMS} (AC Mains) 6 V_{RMS} (AC Mains, ISM Bands)	Pass
Power Frequency Magnetic Field Immunity	IEC 61000-4-8	30 A/m, 50 or 60 Hz	Pass
Voltage Dips & Interruptions Immunity	IEC 61000-4-11	> 95% Dip for 0.5 Cycle 60% Dip for 5 Cycles 30% Dip for 25 Cycles > 95% Dip for 5 seconds	Pass

Test	Standard	Test Level	Results
Radiated Emissions, Vehicles Environment	CISPR 25	Class I	Pass
Radiated Emissions, Airborne Environment	RTCA DO-160G	n/a	Pass

E. Sterilization and Shelf Life Testing of the Disposable Components

1. Sterilization

The LPS is sterilized using ethylene oxide (ETO). ETO sterilization validation was performed per ISO 11135-1:2007 and demonstrates a minimum sterility assurance level (SAL) of 10^{-6}. The lethality of the ETO sterilization process was demonstrated utilizing the overkill concept of sterilization.

Ethylene oxide (ETO) and ethylene chlorohydrin (ECH) residuals were evaluated and determined to be below the maximum allowable limits per ISO 10993-7: 2008, Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals.

OCS™ Lung Solution is sterilized by moist heat. The moist heat sterilization cycle was validated according to Parenteral Drug Association (PDA) Technical Report 1 (TR 1), Validation of Moist Heat Sterilization Processes Cycle Design, Development, Qualification and Ongoing Control, 2007. Volume 61, No. S-1. Sterilization validation demonstrated a minimum SAL of $\leq 10^{-6}$ for the OCS™ Lung Solution.

2. Shelf Life Testing

Package integrity and simulated shipping testing was performed for the LPS and OCS™ Lung Solution to confirm that package integrity can be maintained during shipping. Shelf life testing demonstrates the safety and suitability of the LPS for the labeled 24-month shelf life. Real-time and accelerated shelf life testing supports the safety and suitability of the OCS™ Lung Solution for the labeled 24-month shelf life.

F. Animal Functional Testing

TransMedics performed several animal studies using a porcine model to evaluate the OCS Lung System. Each experiment included retrieving of a swine double lung that was cannulated and instrumented on the OCS Lung System. The OCS™ Lung System was primed with a perfusate solution consisting of pRBCs, OCS™

Lung Solution, and the recommended additives. The organs were preserved on the device for a minimum of 8 hours.

Monitoring Mode was activated at baseline within 1 hr of preservation and after 3 hrs, 6 hrs, and 8 hrs of preservation. At each time point, oxygen saturation in the arterial and venous blood (SaO_2 and SvO2) are recorded; arterial blood gases (ABG) were performed to measure pH, glucose, PaO_2, and PvO_2. The PaO2/FiO2 ratio was calculated from the arterial blood gas pO_2 value.

At the conclusion of the experiments, the double lung was flushed and the organ was then removed from the OCS™ Lung System.

The animal studies demonstrated that the device passed the acceptance criteria, including performance of pre-specified procedures and PaO_2/FiO_2 ratio >300 after 8 hours of preservation, in a simulated clinical environment.

X. SUMMARY OF CLINICAL STUDY

TransMedics conducted the INSPIRE clinical study to establish a reasonable assurance of safety and effectiveness of the OCS™ Lung System for the proposed indication under IDE G100310. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below. Please refer to the Clinical User Guide of the OCS™ Lung System for additional information on the INSPIRE Trial.

A. Study Design

INSPIRE, was a randomized, controlled, multi-center, international, prospective clinical trial to investigate the OCS™ Lung System, compared to the current cold storage standard of care (SOC) for the preservation of donor lungs. The planned sample size of up to 320 subjects was to be enrolled at a maximum of 25 participating sites in the USA, Europe, Australia, and Canada. Four hundred and seven subjects were randomized to either OCS-preserved (treatment arm) or SOC-preserved (control arm) donor lungs with 1:1 randomization ratio. SOC preservation consisted of cold flush and cold ischemic storage of donor lungs the commercially available extracellular preservation solution Perfadex®. Perfusion solution used in the treatment arm preservation was either Perfadex® or TransMedics' proprietary, but equivalent, OCS Lung Solution. Only bilateral donor lungs (as opposed to single donor lungs) were included in the study.

The INSPIRE Trial had oversight by a Data Safety Monitoring Board and utilized a medical monitor for the adjudication of adverse events and Primary Graft Dysfunction (PGD) grading.

1. Clinical Inclusion and Exclusion Criteria

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

Donor Selection Criteria

Inclusion

- < 65 years old
- Normal gas exchange: $P_aO_2/F_iO_2 \geq 300$ at the time of final acceptance of donor lungs
- No active primary pulmonary disease
- Donor lungs suitable for preservation with either OCS or SOC

Exclusion

- Positive serology for Hepatitis B, Hepatitis C, or HIV
- Presence of moderate to severe traumatic lung injury:
  - moderate or massive pneumothorax
  - hemothorax
  - lung contusion as evidenced by chest X-ray, CT-scan, visual inspection, or bronchoscopy
- Presence of confirmed active pneumonia

Recipient Eligibility Criteria

Inclusion

- Registered primary double-lung transplant candidate
- ≥ 18 years old
- Signed, written informed consent document and authorization to use and disclose protected health information

Exclusion

- Prior solid organ or bone marrow transplant
- Single lung recipient
- Multiple organ transplant recipient
- Chronic use of hemodialysis or diagnosis of chronic renal insufficiency

2. Follow-up Schedule

Follow-up data collection was conducted through the initial 7 days, hospital discharge, 30 days, and 6 months post-transplant, with additional long-term data collection at 12 and 24 months.

3. Clinical Endpoints

Primary Effectiveness Endpoint

PGD is a form of acute lung injury that is a known serious complication of lung transplantation. The most severe form (PGD3) has been shown to be correlated with poor short and long-term outcomes, including reduced survival and increased incidence of Bronchiolitis Obliterans Syndrome (BOS).

The initial primary effectiveness endpoint was a composite of patient survival at day 30 post-transplantation and absence of ISHLT PGD3[1] at 72 hours post-transplantation. TransMedic later amended the primary effectiveness endpoint to a composite of patient survival at day 30 post-transplantation and ISHLT PGD3 within 72 hours post-transplantation (i.e., T0, T24, T48, and T72). Results from both the initial and amended primary endpoint will be presented in later sections.

Secondary Effectiveness Endpoints

- Incidence of ISHLT PGD 3 at T72 hours post-lung transplantation
- Incidence of ISHLT PGD 2 or 3 at T72 hours post-lung transplantation
- Patient survival at day 30

Other Clinical Outcomes

- Duration of mechanical ventilation
- Duration of ICU and hospital stay
- Incidence of clinical diagnosis of BOS at 6, 12, and 24 months

Safety Endpoint

The primary safety endpoint was the mean number of lung graft-related serious adverse events (SAE) through the 30 days post-transplantation per subject. A lung graft-related serious adverse event is defined as the occurrence of any of the following four categories of adverse events:

- Biopsy proven moderate to severe acute rejection
- Respiratory failure
- Bronchial anastomotic complication
- Major pulmonary-related infection

Multiple occurrences of SAE of the same category on the same subject within 30 days is counted as one lung graft-related SAE.

1 Christie et al. Report of the ISHLT working group on primary lung graft dysfunction: Part II. Definition. J Heart Lung Transplant 2005;24:1454–1459. See Appendix A for the implementation of the 2005 ISHLT Guideline in the INSPIRE Study

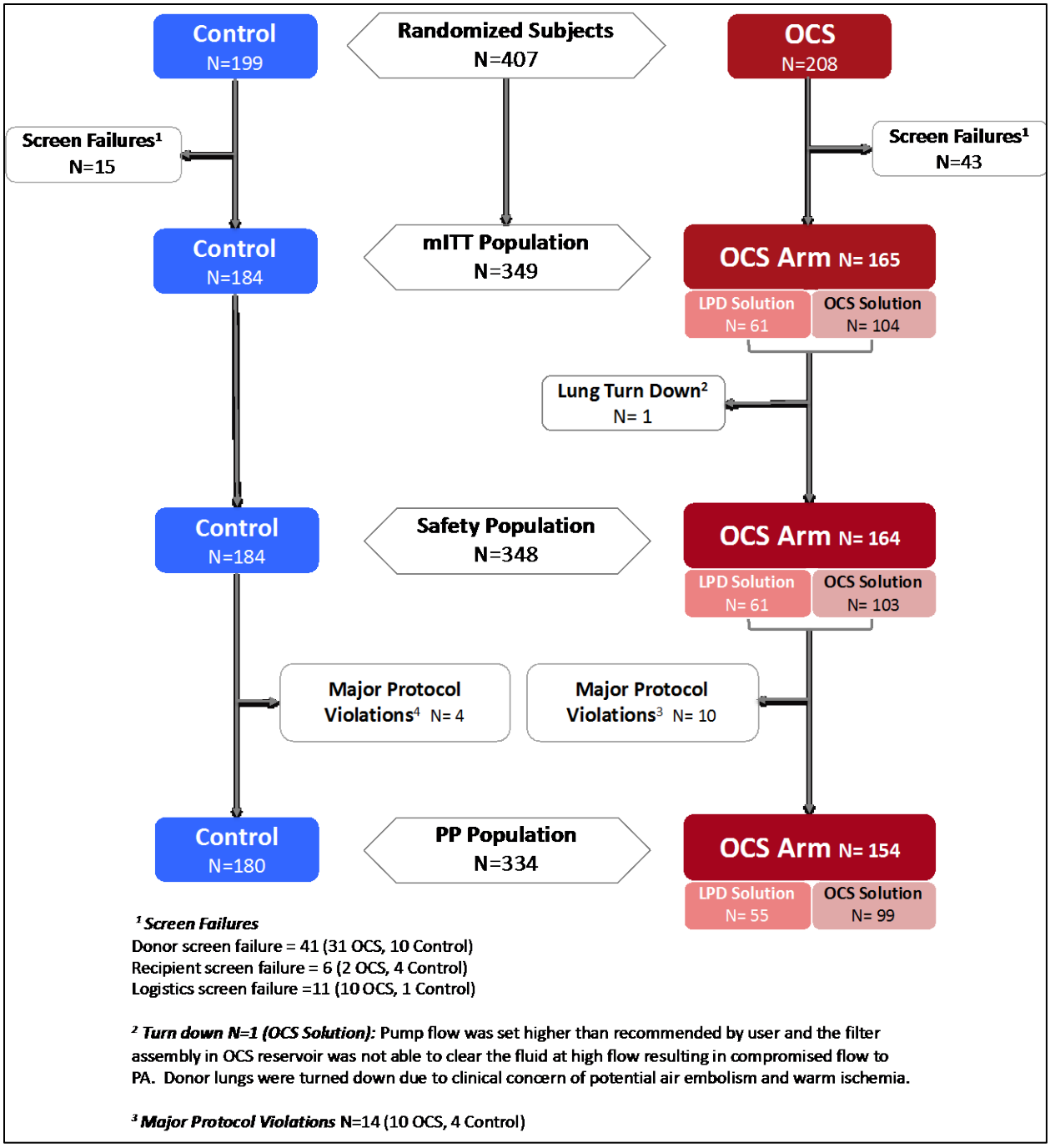
B. Accountability of PMA Cohort

The analysis populations in the INSPIRE Trial are defined as the following:

- **Per-Protocol (PP)**: This population consists of all randomized patients who are transplanted and have no major protocol violations and for whom the eligible donor lung received the complete preservation procedure as per the randomization assignment.
- **Modified Intention-to-Treat (mITT):** This population consists of all randomized patients for whom a matching donor lung has been harvested and determined to be eligible for preservation with either OCS or Control before any attempt has been made to preserve the lung with either OCS or Control.
- **Safety Population (SP)**: This population consists of all patients who were transplanted in the trial with an eligible donor lung that had been preserved with OCS or Control, except for patients randomized to OCS who, due to a decision of the treatment team, were switched to standard therapy (cold storage) before OCS treatment was initiated. The SP is the primary analysis population for safety in the INSPIRE Trial.

The INSPIRE Trial subject consort diagram is shown in Figure 3 below:

Figure 3: INSPIRE Trial Consort Diagram



C. Donor and Recipient Demographics and Baseline Parameters

The recipient demographic and baseline characteristics are shown in Table 5 below:

Table 5: Recipient Demographic and Baseline Characteristics (mITT Population, N=349)

Parameter	Control (N=184)	OCS Arm (N=165)
Age (years)		
N	184	165
Mean ± SD	50.34 ± 13.43	50.45 ± 12.82
Median	55.0	54.0
Minimum - Maximum	18.0 - 72.0	18.0 - 72.0
Gender		
Female	35.9% (66/184)	47.9% (79/165)
Male	64.1% (118/184)	52.1% (86/165)
Ethnicity		
Hispanic or Latino	9.2% (17/184)	13.3% (22/165)
Not Hispanic or Latino	70.7% (130/184)	66.7% (110/165)
Not Applicable	20.1% (37/184)	20.0% (33/165)
Race		
American Indian or Alaskan Native	0.0% (0/183)	0.0% (0/162)
Asian	1.6% (3/183)	1.9% (3/162)
Black or African American	2.7% (5/183)	4.3% (7/162)
Hispanic	3.3% (6/183)	7.4% (12/162)
Native Hawaiian or Other Pacific Islander	0.5% (1/183)	0.0% (0/162)
White	88.0% (161/183)	84.6% (137/162)
Other	3.8% (7/183)	1.9% (3/162)
Weight (kg)		
N	184	165
Mean ± SD	68.78 ± 15.30	67.13 ± 16.65

Parameter	Control (N=184)	OCS Arm (N=165)
Median	68.0	66.0
Minimum - Maximum	37.0 - 112.5	32.0 - 128.0
Type of Status		
Urgent	84.3% (43/51)	82.7% (43/52)
High-Urgent	15.7% (8/51)	17.3% (9/52)
Lung Allocation Score		
N	125	107
Mean ± SD	47.57 ± 18.34	50.54 ± 20.10
Median	40.0	41.0
Minimum - Maximum	1. - 95.0	29.0 - 95.0
Primary Cause of Lung Failure		
Chronic Obstructive Pulmonary Disease	28.8% (53/184)	28.5% (47/165)
Cystic Fibrosis	23.4% (43/184)	20.6% (34/165)
Idiopathic Pulmonary Arterial Hypertension	4.3% (8/184)	8.5% (14/165)
Bronchiectasis	4.9% (9/184)	4.8% (8/165)
Idiopathic Pulmonary Fibrosis	34.8% (64/184)	35.2% (58/165)
Sarcoidosis	4.9% (9/184)	2.4% (4/165)
Other	3.3% (6/184)	4.8% (8/165)
Additional Risk Factors		
Diagnosis of Secondary Pulmonary Hypertension	32.2% (59/183)	40.2% (66/164)
Diagnosis of Heart Failure	7.2% (13/180)	8.5% (14/164)

The donor demographic and baseline characteristics are shown in Table 6 below:

Table 6: Donor Demographic and Baseline Characteristics (mITT Population, N =349)

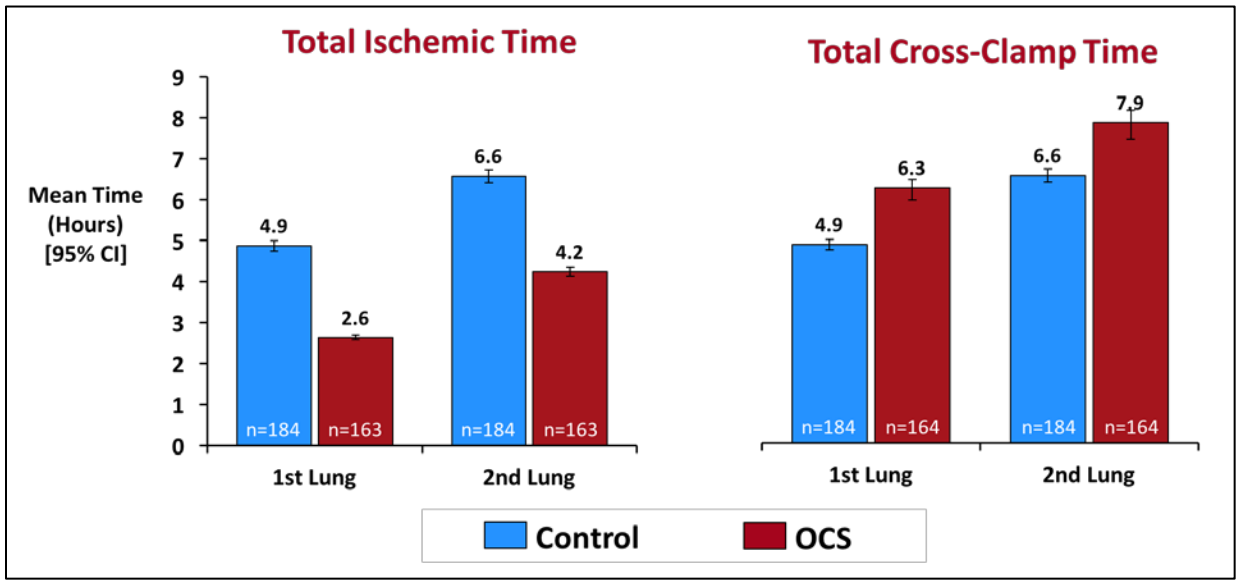
Parameter	Control (N=184)	OCS Arm (N=165)
Donor Age (years)	n=183	n=163
Mean ± SD	40.15 ± 13.70	41.52 ± 14.40
Median	42.0	44.0
Min.-Max.	14.0 - 63.0	13.0 - 64.0
Gender	n=184	N=165
Female	39.7% (73/184)	47.3% (78/165)
Male	60.3% (111/184)	52.7% (87/165)
Donor Final PaO_2/FiO_2 Ratio	n=184	n=163
Mean ± SD	431.73 ± 73.34	441.37 ± 78.89
Median	427.1	435.0
Min.-Max.	301.0 - 642.0	304.0 - 689.0
Abnormal Findings on Physical Examination of Donor Lungs Prior to Retrieval	25.5% (47/184)	36.4% (60/165)
Any Surgical Complications/Tears during Retrieval?	1.4% (2/148)	6.0% (9/151)
Cigarette use (>20 pack years) Continued in Last 6 months	n=183	n=165
Yes	17.5% (32/183)	18.3%(30/164)
No	71.6% (131/183)	69.5% (114/164)
Unknown	10.9% (20/183)	12.2% (20/164)

D. Donor Lung Preservation Characteristics

In the Control cold storage preservation arm, the total cross clamp time and ischemic times are identical. In the OCS Arm, the donor lung is perfused with oxygenated blood perfusate during preservation and ischemic times are limited to time during donor procurement and during surgical re-implantation into the recipient.

As shown in Figure 4 below, the total ischemic time is shorter by approximately 2 hours in the OCS arm than the Control arm, despite longer total cross-clamp time:

Figure 4: Total Cross Clamp and Ischemic Times on Transplanted Lungs (mITT)

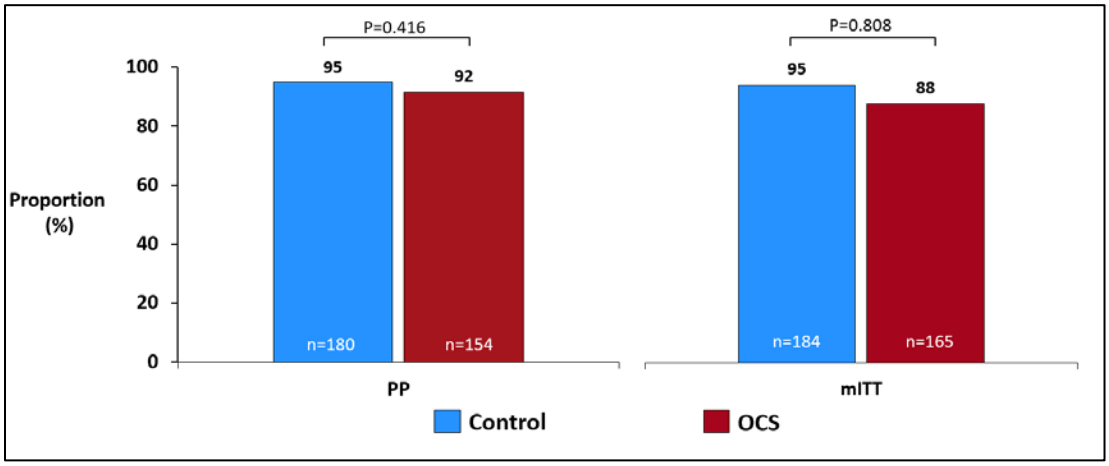


E. Effectiveness and Safety Endpoint Results

1. Primary Effectiveness Endpoint

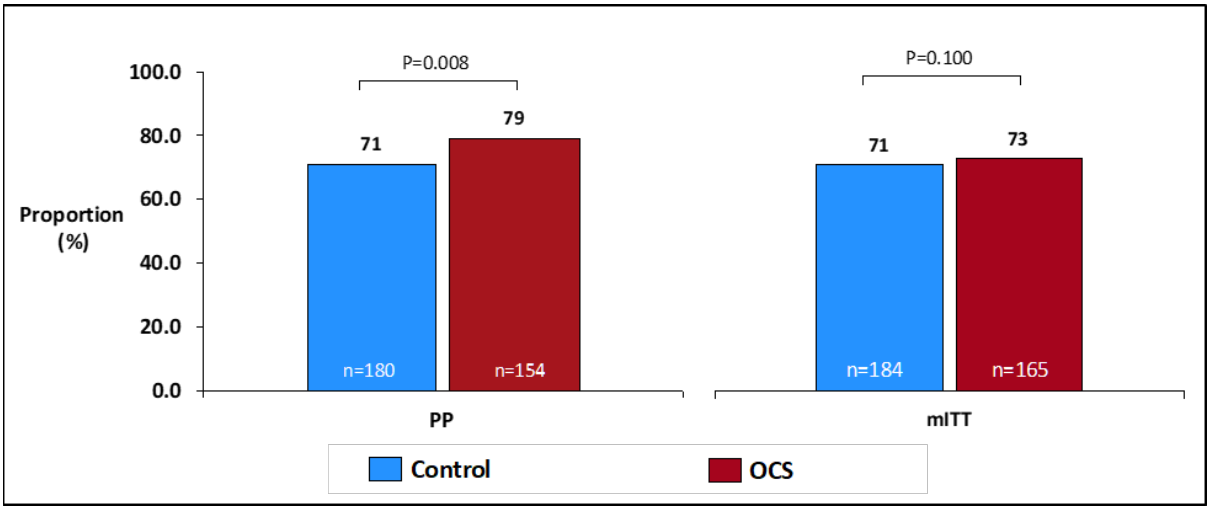
The results for the initial primary effectiveness endpoint of survival at day 30 post-transplantation and freedom from PGD3 at T72 hrs post-transplantation are shown in Figure 5 below. Non-inferiority (4% margin) was not met in the mITT or PP population.

Figure 5: Results for INSPIRE Trial Initial Primary Effectiveness Endpoint -Survival at Day 30 Post-Transplantation and Absence of PGD3 at 72 Hours Post-Transplantation



TransMedics later amended the primary effectiveness endpoint to survival at day 30 post-transplantation and freedom from PGD3 within 72 hrs post-transplantation. The results of the amended primary effectiveness endpoint are shown in Figure 6 below. Non-inferiority (4% margin) was met in the PP population but was not met in the mITT population.

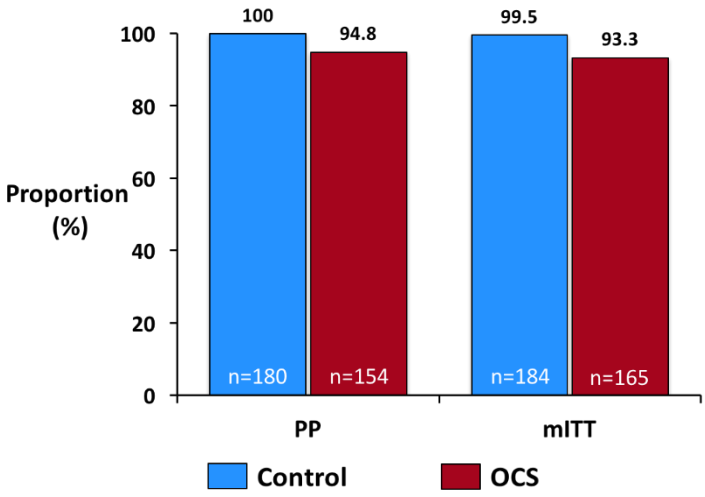
Figure 6: Results for INSPIRE Trial Amended Primary Effectiveness Endpoint – Survival at Day 30 Post-Transplantation and Freedom from PGD3 Within 72 Hours Post-Transplanation



1.1. Day 30 Survival Component of the Primary Effectiveness Endpoint

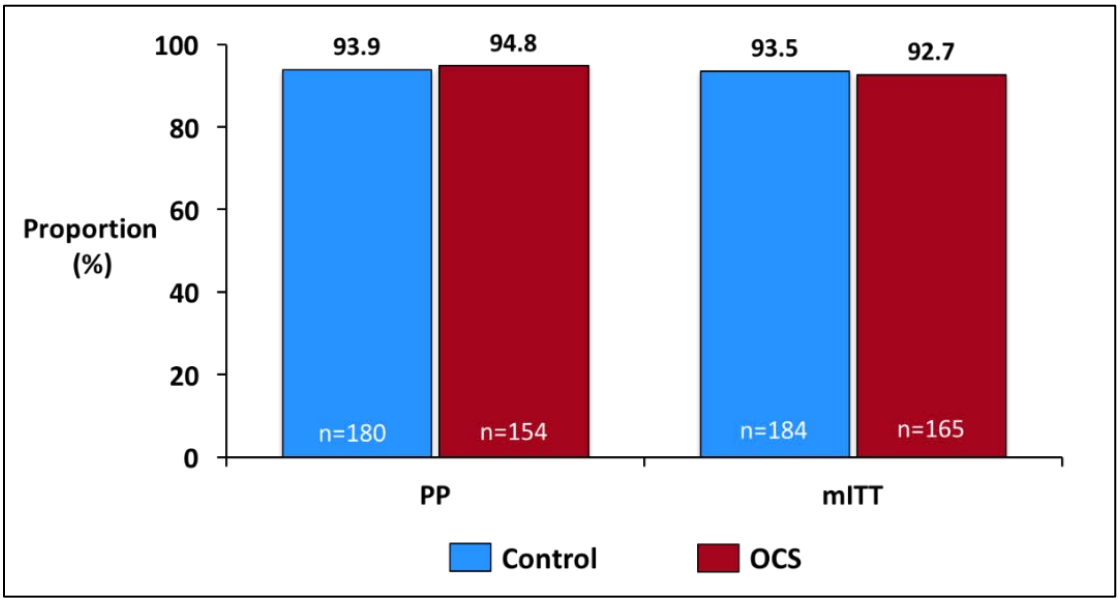
The 30-day survival was lower in the OCS Arm compared to the Control Arm (Figure 7). There were 11 deaths in the OCS Arm and 1 death in the Control Arm within 30 days post-transplantation.

Figure 7: Day 30 Survival



In an adjunctive analysis shown in Figure 8, survival through hospital discharge was similar between the two groups.

Figure 8: In-Hospital Survival



1.2 PGD3 Component of the Primary Effectiveness Endpoint

The results for the PGD3 components of the initial and amended primary effectiveness endpoints are shown in Figure 9 and Figure 10, respectively.

Figure 9: Incidence of PGD3 at 72 hours Post-Transplantation

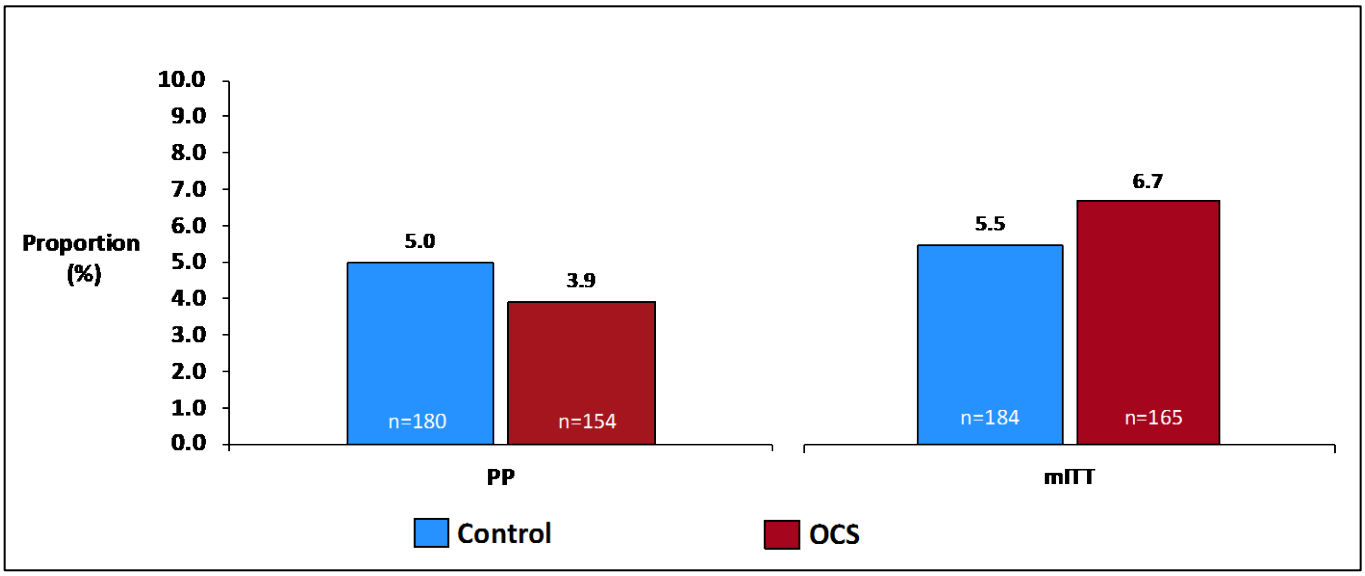
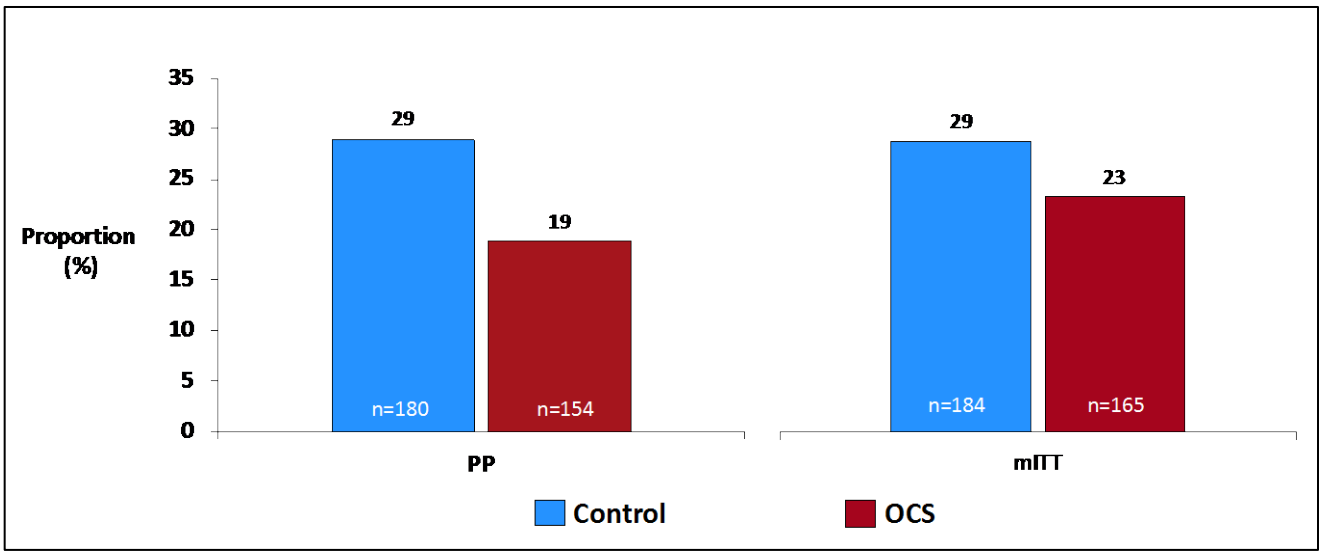


Figure 10: Incidence of PGD3 within 72 hours Post-Transplantation



While the incidence of PGD3 at T72 hours post-transplantation was comparable between the two arms, the OCS Arm showed a reduction in the incidence of PGD3 within the initial 72 hours compared to the Control Arm.

This observed difference was driven predominantlty by T0 grading, as shown in the incidences of PGD3 at T0, T24, T48, and T72 hours post-transplantation (Table 7).

Table 7: Incidence of PGD3 at T0, T24, T48, and T72 hours Post-Transplantation

Analysis Population	Hours Post-Transplantation	Control Arm	OCS Arm
mITT	T0	20.7% (38/184)	17.2% (28/163)
	T24	10.9% (20/184)	13.5% (22/163)
	T48	6.6% (12/183)	9.2% (15/163)
	T72	5.5% (10/183)	6.1% (10/163)
PP	T0	21.1% (38/180)	13.0% (20/154)
	T24	10.6% (19/180)	10.4% (16/154)
	T48	6.7% (12/179)	7.1% (11/154)
	T72	5.0% (9/179)	3.9% (6/154)

2. Secondary Effectiveness Endpoints

The results for the three secondary effectivess endpoints for the PP and mITT population are shown in Table 7 and Table 8, respectively. The analysis of the secondary endpoints was performed using the fixed sequence testing procedure with endpoints tested in order. Statistical testing for non-inferiority was performed for a given secondary endpoint only if non-inferiority was demonstrated for the previous secondary endpoints.

Non-inferiority (5% margin) of OCS compared to Control was demonstrated in the PP population but not in the mITT population for the first secondary effectiveness endpoint, incidence of PGD2 at T72 hours post-transplantation.

Non-inferiority was not demonstrated in either the PP or mITT population for the second (PGD2 or 3 at T72 hours post-transplantation) or the third secondary effectivess endpoint (survival at day 30 post-transplanation).

Table 8: Secondary Effectiveness Endpoints (PP Population)

Parameter	Control (N=180)	OCS Arm (N=154)
Incidence of PGD3 at 72 hours post-transplantation		
Proportion (π) (%) (n/N)[1]	5.0% (9/179)	3.9% (6/154)
95% CI for Proportion[2]	(2.3%, 9.3%)	(1.4%, 8.3%)
π_{ocs} - $\pi_{Control}$ (%) (one-sided 95% CI)[3]		-1.1% (-∞, 2.6%)
p-value of non-Inferiority test[4]		0.0033
Incidence of PGD2 or PGD3 at 72 hours post-transplantation		
Proportion (π) (%) (n/N)[1]	10.6% (19/179)	13.0% (20/154)
95% CI for Proportion[2]	(6.5%, 16.1%)	(8.1%, 19.3%)
π_{ocs} - $\pi_{Control}$ (%) (one-sided 95% CI)[3]		2.4% (-∞, 8.2%)
p-value of non-Inferiority test[4]		0.0746
Patient survival at day 30 post-transplantation		
Proportion (π) (%) (n/N)[1]	100.0% (180/180)	94.8% (146/154)
	(98.0%, 100.0%)	(90.0%, 97.7%)
π_{ocs} - $\pi_{Control}$ (%) (one-sided 95% CI)[3]		5.2% (-∞, 8.1%)
p-value of non-Inferiority test[4]		N/A

[1] π = n/N *100% = simple proportion. [2] The 95% confidence interval was calculated based on the Clopper-Pearson method. [3] The 95% upper confidence limit is for the difference between the two population proportions (π_{OCS}-$\pi_{Control}$) for secondary endpoints 1 and 2. [4] The p-value is based on Wald Method. The non-inferiority margin is 5%, 7.5% and 4% for secondary endpoint 1, 2, and 3, respectively. N/A – Not applicable

Table 9: Secondary Effectiveness Endpoints (mITT Population)

Parameter	Control (N=184)	OCS Arm (N=165)
Incidence of PGD3 at 72 hours post-transplantation		
Proportion (π) (%) (n/N)[1]	5.5% (10/183)	6.7% (11/164)
95% CI for Proportion[2]	(2.7%, 9.8%)	(3.4%, 11.7%)
π_{ocs} - $\pi_{Control}$ (%) (one-sided 95% CI)[3]		1.2% (-∞, 5.5%)
p-value of non-Inferiority test[4]		0.0724

Parameter	Control (N=184)	OCS Arm (N=165)
Incidence of ISHLT PGD2 or PGD3 at 72 hours post-transplantation		
Proportion (π) (%) (n/N)[1]	10.9% (20/183)	16.5% (27/164)
95% CI for Proportion[2]	(6.8%, 16.4%)	(11.1%, 23.0%)
π_{ocs} - $\pi_{Control}$ (%) (one-sided 95% CI)[3]		5.5% (-∞, 11.6%)
p-value of non-Inferiority test[4]		N/A
Patient survival at day 30 post-transplantation		
Proportion (π) (%) (n/N)[1]	99.5% (183/184)	92.7% (153/165)
95% CI for Proportion[2]	(97.0%, 100.0%)	(87.6%, 96.2%)
π_{ocs} - $\pi_{Control}$ (%) (one-sided 95% CI)[3]		6.7% (-∞, 10.2%)
p-value of non-Inferiority test[4]		N/A

[1] π = n/N *100% = simple proportion. [2] The 95% confidence interval was calculated based on the Clopper-Pearson method. [3] The 95% upper confidence limit is for the difference between the two population proportions (π_{OCS}-$\pi_{Control}$) for secondary endpoints 1 and 2. [4] The p-value is based on Wald Method. The non-inferiority margin is 5%, 7.5% and 4% for secondary endpoint 1, 2, and 3, respectively. N/A – Not applicable

3. Safety Endpoint

The results for the safety endpoint (i.e., the average number of Lung Graft-Related Serious Adverse Events (LGRSAEs) through 30 days post-transplant) are shown in Table 9. Non-inferiority (7% margin) of the OCS compared to Control was demonstrated.

Table 10: Safety Endpoint Analysis – (Average Number of LGRSAEs through the 30 days post-transplantation per patient)

INSPIRE Combined Cohort (n=349)	Control N=184	OCS N=164
Lung-graft related SAEs, n (%)	45 (24.5)	40 (24.4)
Mean ± SD	0.29 ± 0.54	0.26 ± 0.48
Non-Inferiority p-value		0.042
Type of Lung-graft related SAEs, n (%)		
Acute Rejection	4 (2)	2 (1)
Respiratory Failure*	16 (9)	23 (14)
Bronchial Anastomotic Complication	4 (2)	0
Major Pulmonary-Related Infection	29 (16)	18 (11)

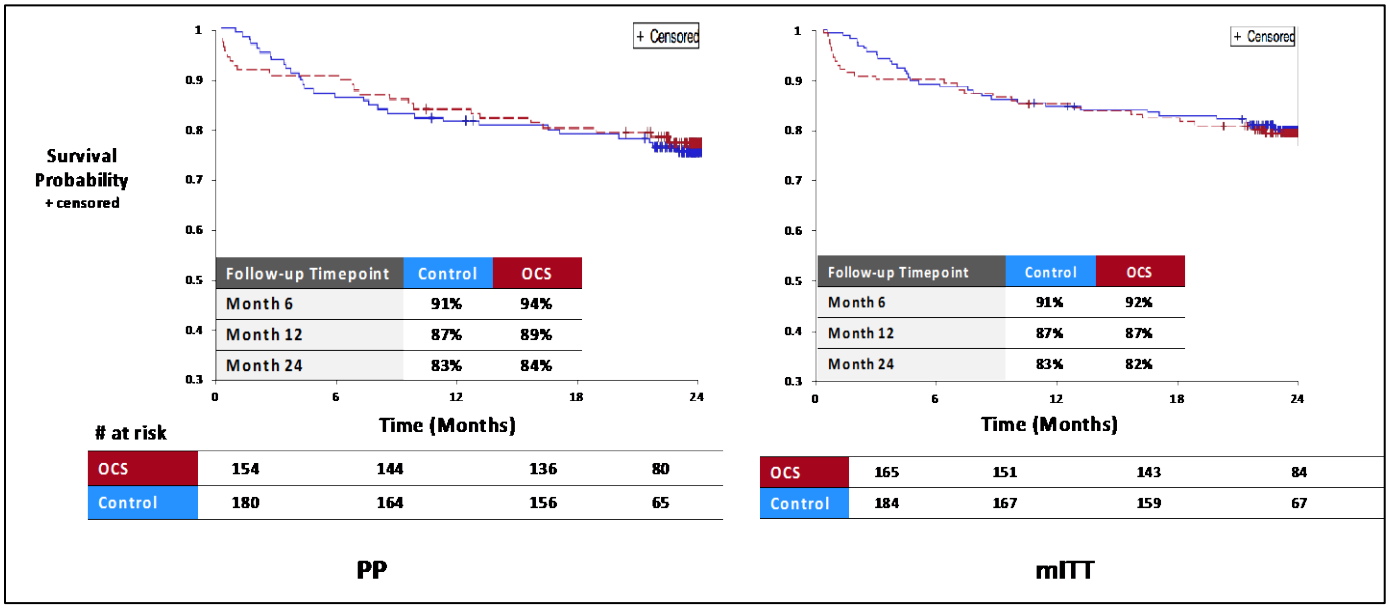
*Need for re-intubation, tracheostomy or the inability to discontinue ventilator support within 4 days post-transplant

F. Other Clinical Outcomes

1. Long-Term Survival through 24 Months

   Kaplan-Meier (K-M) survival analyses through 24 months for the PP and mITT populations are shown in Figure 11. The survival of the two arms was comparable at 24 months of follow-up.

Figure 11: K-M Survival for OCS and Control groups at 24 Months



2. Freedom from BOS and BOS-Free Survival through 24 Months

   The results for patients who were free from BOS (Figure 12) and for those who surived and were free from BOS (Figure 13) were overall similar between the two arms. Transmedics will evaluate long-term BOS up to 5 years post-transplantation in a post-market study.

Figure 12: BOS-Free Probability through 24 Months

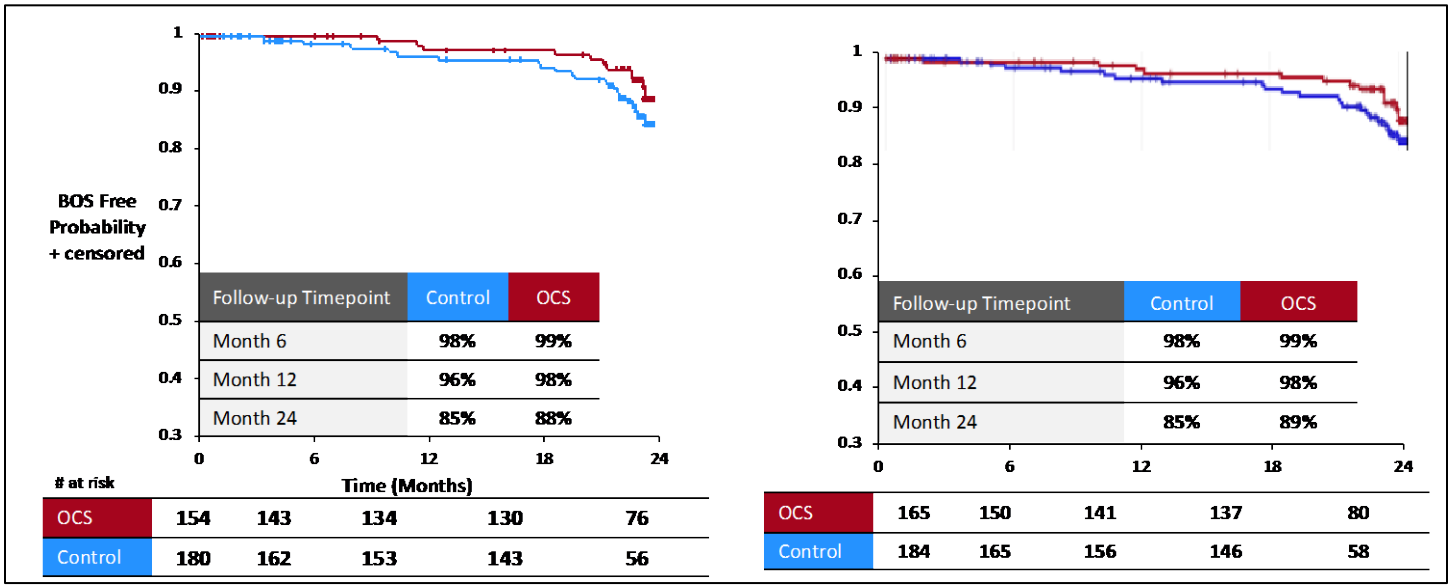
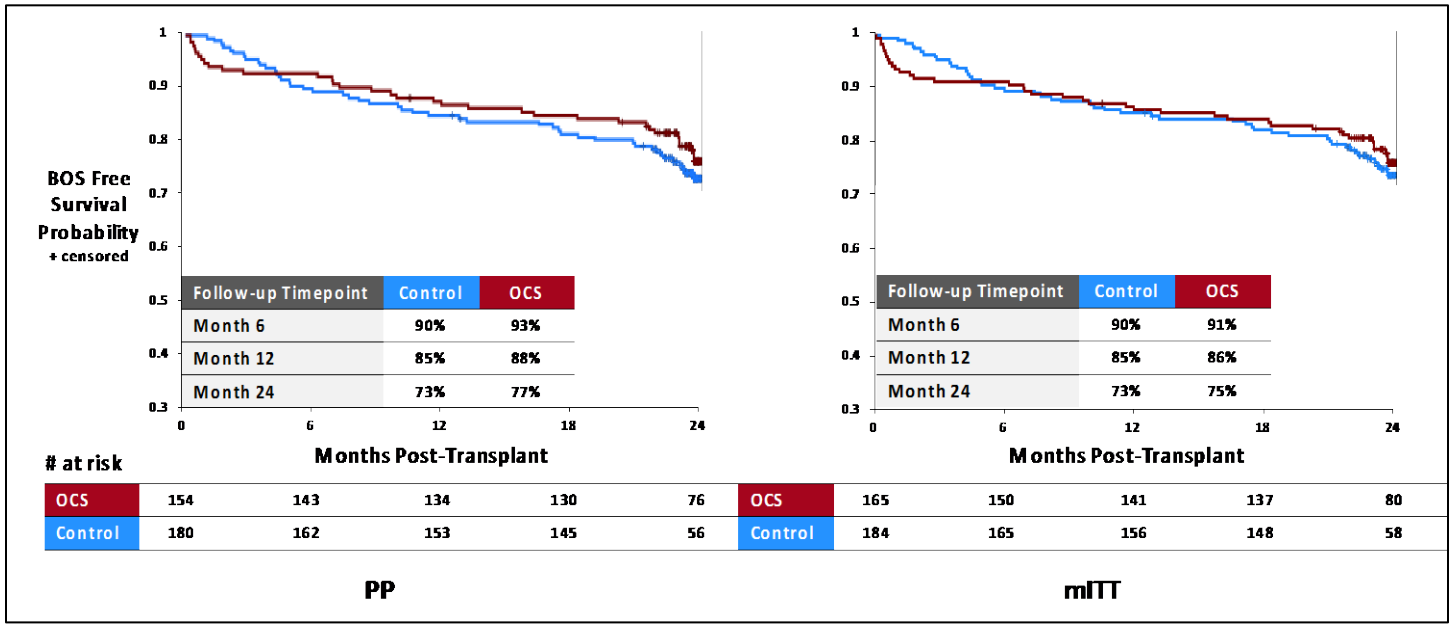


Figure 13: BOS-Free Survival Probability through 24 Months



3. Mechanical Ventiatlion, ICU Stay and Hospital Stay

   Although not statistically significant, the OCS Arm showed some reduction in time on ventilation, ICU time, and hospital stay post-transplanation (Figure 14 and Figure 15).

Figure 14: Ventilation Time, ICU Time, and Hospitalization (PP Population)

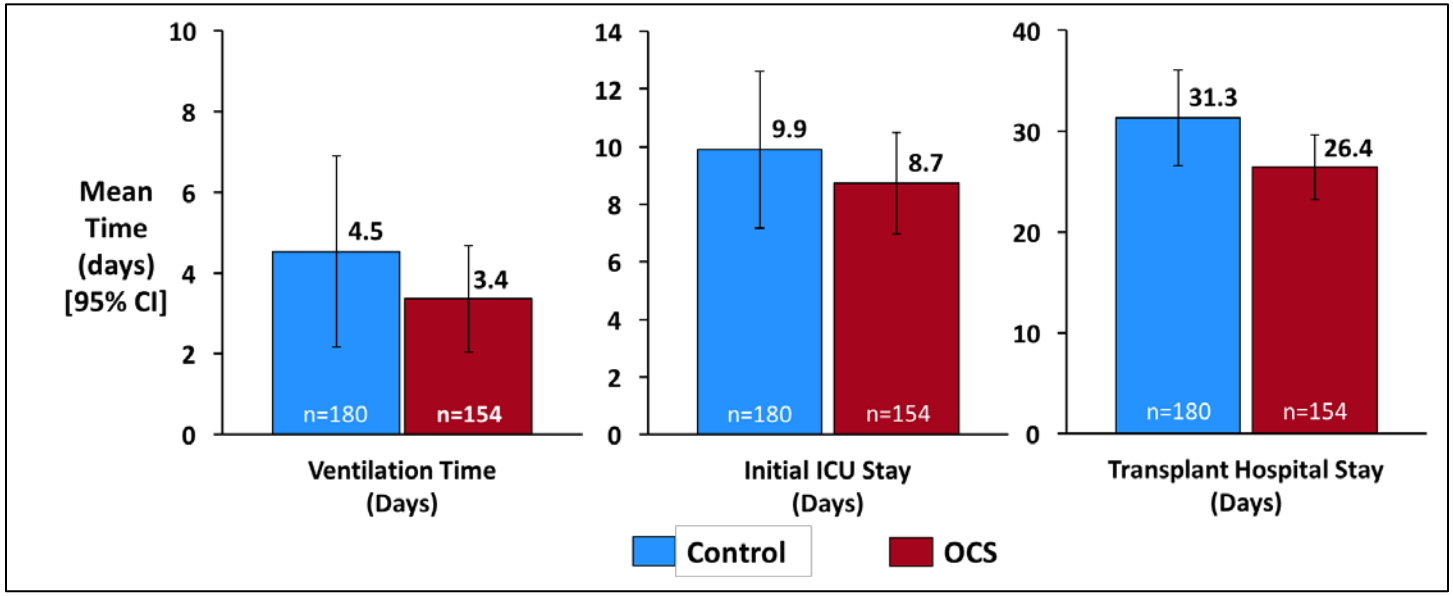
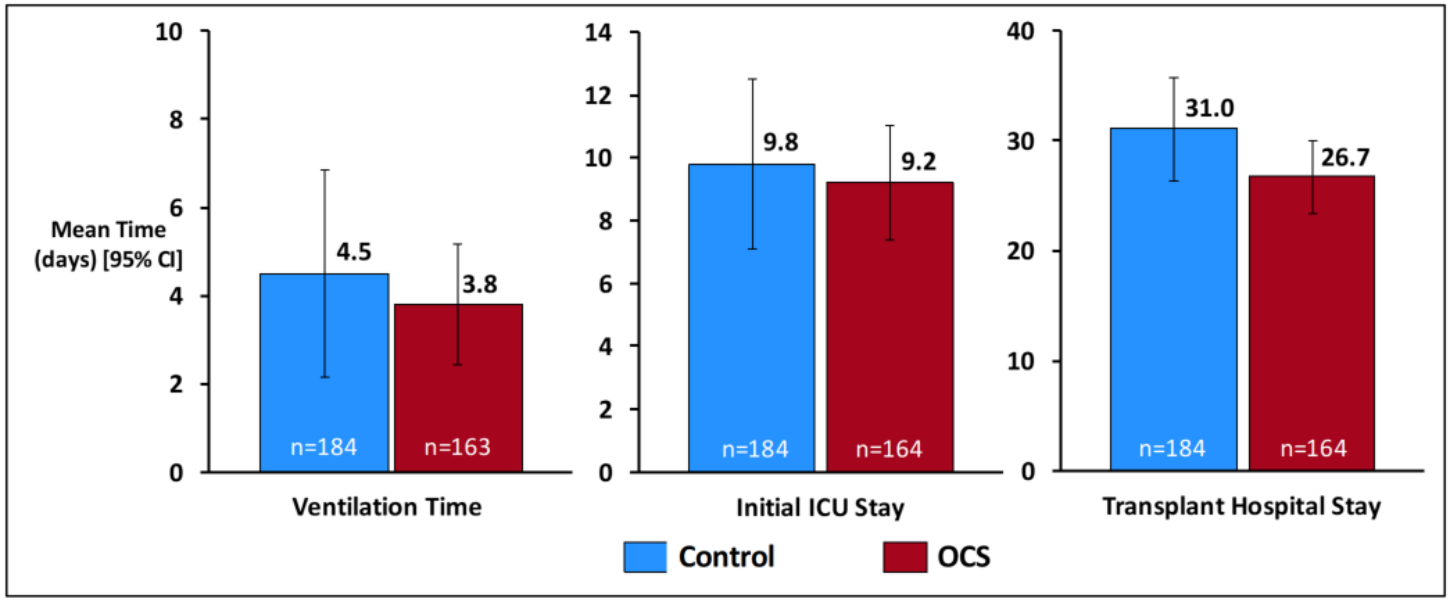


Figure 15: Ventilation Time, ICU Time, and Hospitalization (mITT Population)



G. Device Malfunctions

A summary of the device malfunctions that occurred during the INSPIRE Trial is provided in Table 10 below. Twelve (12) malfunctions occurred. In 2 subjects, the malfunction occurred prior to donor organ retrieval, and the subjects were transplanted off study using cold storage. The other 10 patients were analyzed in the study. One malfunction (reduced reservoir volume at high flow rate) led to loss of a donor organ. This patient later received an organ preserved with cold storage.

Table 11: Summary of Device Malfunctions and User Errors

Malfunctions/User Errors & Learning Curve	Total N (12)	Loss of Lung	Txed off Study - Screen Failure	Txed and Analyzed in INSPIRE
Reduced reservoir volume at high pump flow	4	1	0	3
User Errors • Premature unlocking of LPM • Failure to secure port cover during bronchoscopy • Failure to install LPM properly (2)	4	0	0	4
Battery failure	1	0	0	1
Broken gas port	1	0	0	1
Perfusate leak from LPM Prior to Lung Retrieval or Instrumentation on OCS™ Lung System	1	0	1	0
Unable to power up device Prior to Lung Retrieval or Instrumentation on OCS™ Lung System	1	0	1	0
TOTAL	**12**	**1**	**2**	**9**

TransMedics has addressed the observed malfunctions with design and manufacturing improvements that were implemented and used during the INSPIRE Trial to minimize the potential for recurrence as described below:

- The filter assembly components of the LPM were modified to improve the efficiency and capacity of these sub-components, thereby improving perfusate flow from the organ chamber to the reservoir.
- The perfusion module was modified to improve the engagement with the OCS™ Lung Console. This design change mitigated against the user inadvertently disconnecting the perfusion module from the OCS™ Lung Console.
- The port on the gas regulator was changed to resist breakage.
- The reservoir vent design and the manufacturing method of the perfusion module frame were improved to reduce the likelihood of leaks at the tubing connection points to the frame.

- The failure of the OCS battery to deliver charge was addressed by a strict battery shelf life requirement and preventive maintenance.

H. Summary of Adverse Events

An overall summary of adverse events is presented in Table 12 below and the serious adverse events (SAEs) are shown in Table 13 below.

Table 12: Adverse Events by Type of Event; Safety Population (N=348)

Parameter	Control (N=184)	OCS Arm (N=164)	OCS Solution (N=103)
Patients with Any Type of Adverse Events	152 (82.6%)	136 (82.9%)	86 (83.5%)
Patients with Adverse Events Definitely Related to OCS or Control	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patients with Adverse Events Probably Related to OCS or Control	0 (0.0%)	1 (0.6%)	1 (1.0%)
Patients with Adverse Events Possibly Related to OCS or Control	5 (2.7%)	5 (3.0%)	2 (1.9%)
Patients with Adverse Events Unlikely Related to OCS or Control	57 (31.0%)	59 (36.0%)	35 (34.0%)
Patients with Adverse Events Unrelated to OCS or Control	131 (71.2%)	113 (68.9%)	70 (68.0%)
Patients with Adverse Events Unanticipated	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patients with Any Serious Adverse Events	116 (63.0%)	92 (56.1%)	58 (56.3%)
Patients with Any Severe Adverse Events	54 (29.3%)	51 (31.1%)	31 (30.1%)
Deaths up to 24 months[1]	31 (16.8%)	28 (17.1%)	19 (18.4%)

[1] OCS Arm death count includes Subject 31-030 who was withdrawn from study first, then followed by re-transplantation and died afterwards. All Adverse Events were up to 30 days post-transplantation or initial hospital discharge, LGR SAEs were up to 6 months post-transplantation.

Table 13: Adjudicated Serious Adverse Events by Preferred Term that occurred in ≥ 1% of Subjects; Safety Population (N=348)

System Organ Class and Preferred Term		Control n (%)		OCS Arm n (%)		OCS Solution n (%)	
		Patients (N=184)	**Events (N=247)**	**Patients (N=164)**	**Events (N=192)**	**Patients (N=103)**	**Events (N=118)**
Total		**116 (63.0)**	**247 (100.0)**	**92 (56.1)**	**192 (100.0)**	**58 (56.3)**	**118 (100.0)**
Respiratory, thoracic and mediastinal disorders		**57 (31.0)**	**74 (30.0)**	**47 (28.7)**	**59 (30.7)**	**29 (28.2)**	**37 (31.4)**
	Respiratory failure	17 (9.2)	18 (7.3)	20 (12.2)	22 (11.5)	13 (12.6)	15 (12.7)
	Pleural effusion	12 (6.5)	12 (4.9)	6 (3.7)	7 (3.6)	3 (2.9)	4 (3.4)
	Pneumothorax	12 (6.5)	12 (4.9)	5 (3.0)	6 (3.1)	3 (2.9)	4 (3.4)
	Haemothorax	9 (4.9)	9 (3.6)	7 (4.3)	8 (4.2)	2 (1.9)	3 (2.5)
	Bronchostenosis	4 (2.2)	5 (2.0)	5 (3.0)	5 (2.6)	3 (2.9)	3 (2.5)
	Pulmonary embolism	4 (2.2)	4 (1.6)	3 (1.8)	3 (1.6)	2 (1.9)	2 (1.7)
	Bronchial disorder	3 (1.6)	4 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Bronchial secretion retention	2 (1.1)	2 (0.8)	2 (1.2)	2 (1.0)	0 (0.0)	0 (0.0)
	Acute respiratory failure	1 (0.5)	1 (0.4)	2 (1.2)	2 (1.0)	2 (1.9)	2 (1.7)
	Chylothorax	2 (1.1)	2 (0.8)	1 (0.6)	1 (0.5)	1 (1.0)	1 (0.8)
	Bronchopleural fistula	2 (1.1)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations		**56 (30.4)**	**72 (29.1)**	**38 (23.2)**	**43 (22.4)**	**26 (25.2)**	**29 (24.6)**

System Organ Class and Preferred Term		Control n (%)		OCS Arm n (%)		OCS Solution n (%)	
		Patients (N=184)	Events (N=247)	Patients (N=164)	Events (N=192)	Patients (N=103)	Events (N=118)
	Pneumonia	20 (10.9)	20 (8.1)	14 (8.5)	15 (7.8)	10 (9.7)	11 (9.3)
	Lung infection	7 (3.8)	8 (3.2)	3 (1.8)	3 (1.6)	2 (1.9)	2 (1.7)
	Bronchopneumonia	3 (1.6)	3 (1.2)	5 (3.0)	5 (2.6)	3 (2.9)	3 (2.5)
	Infection	5 (2.7)	5 (2.0)	3 (1.8)	3 (1.6)	1 (1.0)	1 (0.8)
	Bronchitis	4 (2.2)	4 (1.6)	1 (0.6)	1 (0.5)	0 (0.0)	0 (0.0)
	Bronchopulmonary aspergillosis	4 (2.2)	4 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Lung infection pseudomonal	1 (0.5)	1 (0.4)	3 (1.8)	3 (1.6)	2 (1.9)	2 (1.7)
	Respiratory tract infection	2 (1.1)	2 (0.8)	2 (1.2)	2 (1.0)	2 (1.9)	2 (1.7)
	Sepsis	4 (2.2)	4 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Staphylococcal infection	3 (1.6)	3 (1.2)	1 (0.6)	1 (0.5)	1 (1.0)	1 (0.8)
	Wound infection	4 (2.2)	4 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Diverticulitis	2 (1.1)	2 (0.8)	1 (0.6)	1 (0.5)	1 (1.0)	1 (0.8)
	Aspergillosis	0 (0.0)	0 (0.0)	2 (1.2)	2 (1.0)	1 (1.0)	1 (0.8)
	Clostridium difficile colitis	2 (1.1)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Cytomegalovirus infection	2 (1.1)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Pseudomonas infection	0 (0.0)	0 (0.0)	2 (1.2)	2 (1.0)	2 (1.9)	2 (1.7)
	Septic shock	2 (1.1)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

System Organ Class and Preferred Term		Control n (%)		OCS Arm n (%)		OCS Solution n (%)	
		Patients (N=184)	**Events (N=247)**	**Patients (N=164)**	**Events (N=192)**	**Patients (N=103)**	**Events (N=118)**
Cardiac disorders		**16 (8.7)**	**17 (6.9)**	**15 (9.1)**	**20 (10.4)**	**11 (10.7)**	**13 (11.0)**
	Atrial fibrillation	6 (3.3)	7 (2.8)	7 (4.3)	7 (3.6)	5 (4.9)	5 (4.2)
	Cardiac arrest	0 (0.0)	0 (0.0)	5 (3.0)	6 (3.1)	4 (3.9)	4 (3.4)
	Arrhythmia	2 (1.1)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Atrial flutter	2 (1.1)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Cardiac failure congestive	0 (0.0)	0 (0.0)	2 (1.2)	2 (1.0)	1 (1.0)	1 (0.8)
	Cardiac tamponade	2 (1.1)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders		**13 (7.1)**	**13 (5.3)**	**13 (7.9)**	**13 (6.8)**	**7 (6.8)**	**7 (5.9)**
	Renal failure acute	6 (3.3)	6 (2.4)	11 (6.7)	11 (5.7)	7 (6.8)	7 (5.9)
	Renal failure	7 (3.8)	7 (2.8)	2 (1.2)	2 (1.0)	0 (0.0)	0 (0.0)
Vascular disorders		**9 (4.9)**	**10 (4.0)**	**11 (6.7)**	**14 (7.3)**	**6 (5.8)**	**7 (5.9)**
	Haemorrhage	5 (2.7)	5 (2.0)	5 (3.0)	5 (2.6)	3 (2.9)	3 (2.5)
	Deep vein thrombosis	1 (0.5)	1 (0.4)	4 (2.4)	4 (2.1)	2 (1.9)	2 (1.7)
	Ischaemia	0 (0.0)	0 (0.0)	2 (1.2)	2 (1.0)	1 (1.0)	1 (0.8)
Injury, poisoning and procedural complications		**10 (5.4)**	**10 (4.0)**	**11 (6.7)**	**11 (5.7)**	**7 (6.8)**	**7 (5.9)**
	Post-procedural haemorrhage	1 (0.5)	1 (0.4)	6 (3.7)	6 (3.1)	3 (2.9)	3 (2.5)
	Wound dehiscence	2 (1.1)	2 (0.8)	3 (1.8)	3 (1.6)	3 (2.9)	3 (2.5)

System Organ Class and Preferred Term		Control n (%)		OCS Arm n (%)		OCS Solution n (%)	
		Patients (N=184)	**Events (N=247)**	**Patients (N=164)**	**Events (N=192)**	**Patients (N=103)**	**Events (N=118)**
	Procedural complication	2 (1.1)	2 (0.8)	1 (0.6)	1 (0.5)	0 (0.0)	0 (0.0)
Gastrointestinal disorders		**13 (7.1)**	**17 (6.9)**	**2 (1.2)**	**2 (1.0)**	**1 (1.0)**	**1 (0.8)**
	Impaired gastric emptying	2 (1.1)	2 (0.8)	1 (0.6)	1 (0.5)	1 (1.0)	1 (0.8)
	Diarrhoea	2 (1.1)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Gastrointestinal haemorrhage	2 (1.1)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Large intestine perforation	2 (1.1)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immune system disorders		**12 (6.5)**	**12 (4.9)**	**6 (3.7)**	**6 (3.1)**	**5 (4.9)**	**5 (4.2)**
	Lung transplant rejection	12 (6.5)	12 (4.9)	5 (3.0)	5 (2.6)	4 (3.9)	4 (3.4)
Nervous system disorders		**8 (4.3)**	**8 (3.2)**	**8 (4.9)**	**9 (4.7)**	**4 (3.9)**	**4 (3.4)**
	Cerebrovascular accident	0 (0.0)	0 (0.0)	4 (2.4)	4 (2.1)	1 (1.0)	1 (0.8)
	Encephalopathy	2 (1.1)	2 (0.8)	1 (0.6)	1 (0.5)	0 (0.0)	0 (0.0)
	Brain oedema	2 (1.1)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Convulsion	2 (1.1)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions		**5 (2.7)**	**5 (2.0)**	**3 (1.8)**	**3 (1.6)**	**3 (2.9)**	**3 (2.5)**
Blood and lymphatic system disorders		**1 (0.5)**	**1 (0.4)**	**3 (1.8)**	**3 (1.6)**	**1 (1.0)**	**1 (0.8)**
Psychiatric disorders		**4 (2.2)**	**4 (1.6)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
	Delirium	2 (1.1)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

System Organ Class and Preferred Term	Control n (%)		OCS Arm n (%)		OCS Solution n (%)	
	Patients (N=184)	Events (N=247)	Patients (N=164)	Events (N=192)	Patients (N=103)	Events (N=118)
Metabolism and nutrition disorders	2 (1.1)	2 (0.8)	1 (0.6)	1 (0.5)	1 (1.0)	1 (0.8)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	2 (1.2)	2 (1.0)	1 (1.0)	1 (0.8)
Surgical and medical procedures	0 (0.0)	0 (0.0)	2 (1.2)	2 (1.0)	1 (1.0)	1 (0.8)

I. Pediatric Extrapolation

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

J. 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 21 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

FDA had significant concerns regarding imbalances in the post-randomization screen failures and protocol violations between the two treatment groups. Despite 1:1 randomization, 74% of the 58 total post-randomization screen failures occurred in the OCS arm. Numerous screen failures whose basis for determinations were either eligibility criteria not specified in the protocol or logistical matters unrelated to an eligible donor-recipient match. Off-study transplantations after determinations of trial ineligibility because of active donor lung disease only occurred in the OCS arm. Imbalances in protocol violations (11 in the OCS Arm vs. 4 in the Control Arm) were also evident. All 11 of the OCS Arm subjects who were excluded from the mITT population were endpoint failures. In addition, FDA had significant concerns regarding TransMedics' changing the primary effectiveness endpoint and primary analysis population after interim analyses and majority of trial enrollment had already been completed. Together, these issues introduce substantial uncertainty regarding the interpretability and reliability of the data.

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

A. Panel Meeting Recommendation

At an advisory meeting held on May 16, 2017, the Gastroenterology-Urology Devices Panel voted 11-2 that there is reasonable assurance the device is safe, 8-5 that there is reasonable assurance that the device is effective, and 9-4 that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication. Additional information on the Advisory Panel can be found at the following website: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Gastroenterology-UrologyDevicesPanel/ucm556140.htm

B. FDA's Post-Panel Action

After the Panel, FDA and TransMedics held numerous discussions regarding post-approval study and labeling requirements.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The amended primary effectiveness endpoint evaluated a composite of Survival at Day 30 Post-Transplantation and Freedom from PGD3 Within 72 Hours Post-Transplanation, comparing the OCS™ Lung System to SOC. The endpoint was designed to demonstrate non-inferiority with a margin of 4%. Non-inferiority was demonstrated in the Per-Protocol (PP) population for OCS (79%) vs. Control (71%), p=0.008. While the same analysis in the pre-specified mITT population failed to reach statistical significance, results trended in the same direction as the PP analysis (73% vs. 71% for OCS vs. control, respectively, p=0.10). When the components of the composite primary effectiveness endpoint were considered individually: 1) the OCS Arm showed a reduction in the incidence of PGD3 within the initial 72 hours compared to the Control Arm, and 2) the 30-day survival was lower in the OCS Arm compared to the Control Arm; although, the majority of the Panel felt that the early mortality would not be a significant factor in how they interpret the results. Further, an adjunctive analysis showed that survival through hospital discharge was similar between the two groups. Additionally, the Panel nearly unanimously agreed that the 2-year survival and BOS rates were comparable between the two study arms. While these data suffer from similar reliability issues as the INSPIRE data in general, they do provide support that the OCS™ Lung System is non-inferior to SOC when considering longer-term outcomes.

For the initial primary effectiveness endpoint of survival at day 30 and freedom from PGD3 at T72 hours post-transplantation, non-inferiority was not shown in the mITT or PP populations.

B. Safety Conclusions

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

The primary safety endpoint was the mean number of lung graft-related serious adverse events (LGRSAEs) through the 30 days post-transplantation per subject. The endpoint was designed to demonstrate non-inferiority with a margin of 7%. Non-inferiority was demonstrated with the number and percentage of subjects experiencing an LGRSAE in the OCS group (n=40, 24.4%) vs. Control group (n=45, 24.5%) (p=0.042).

The safety results discussed in this section, along with the results discussed in the effectiveness section above (many of which could also be considered to be safety outcomes) demonstrate comparability between the OCS group and SOC, indicating the OCS™ Lung System is a reasonable alternative to the current SOC.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The OCS™ Lung System demonstrated non-inferiority compared to SOC in terms of the amended primary effectiveness endpoint of Survival at Day 30 Post-Transplantation and Freedom from PGD3 Within 72 Hours Post-Transplanation (PP population). Survival to hospital discharge was similar between the two groups. Further, longer-term (2-year) survival and BOS rates were comparable between the two study arms. The primary safety endpoint demonstrated non-inferiority compared to SOC.

An important additional factor considered in determining probable risks and benefits for the OCS™ Lung System device included uncertainty. The clinical study was a randomized, controlled, multi-center, prospective clinical trial. However, changes to the protocol while the study was ongoing increased the likelihood of biased outcomes and created challenges regarding the interpretation of the study results. Although the panel expressed concern about the conduct of the study, specifically referring to the inappropriate nature of changes in the primary endpoint after more than 70% of patient enrollment was complete, the majority of the panel vote reflected a favorable Benefit Risk profile.

In conclusion, given the available information above, the data support that for the OCS™ Lung System which is indicated for use as a portable organ perfusion, ventilation, and monitoring medical device intended to preserve standard criteria donor lungs in a near physiologic, ventilated, and perfused state for double lung transplantation, the probable benefits outweigh the probable risks. This conclusion is supported by the Panel's deliberations and recommendation, along the conditions of approval that include a post-approval study, labeling and training requirements, as well as a patient decision checklist.

This submission did not include specific information on patient perspectives for this device.

D. Overall Conclusions

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

The overall safety and effectiveness data indicate that the OCS™ Lung System is non-inferior to SOC. Short term (the composite of Survival at Day 30 Post-Transplantation and Freedom from PGD3 Within 72 Hours) and longer-term (2-year survival and BOS rates) results were comparable between the device and SOC. This determination is consistent with the Panel's recommendation in combination with the conditions of approval that include a post-approval study, labeling and training requirements, as well as a patient decision checklist.

XIV. CDRH DECISION

CDRH issued an approval order on March 22, 2018. The final conditions of approval cited in the approval order are described below.

1. The INSPIRE Continuation Post-Approval Study:

The INSPIRE Continuation PAS is a two-arm observational study intended to evaluate long-term outcomes of the INSPIRE Trial patients. The study population will include all U.S INSPIRE patients and all OUS INSPIRE patients who consent to participation. The primary effectiveness endpoint is BOS-free survival through 5 years after transplantation. The follow-up period for all patients will be up to 5 years. Interim PAS reports will be submitted to FDA at 6, 12, 24, and 36 months after PMA approval. A final report will be submitted to FDA when all patients complete their 5-year follow-up.

2. The OCS Lung Thoracic Organ Perfusion (TOP) PAS Registry:

The TOP PAS is a prospective, single-arm, multi-center, observational study designed to evaluate the short- and long-term safety and effectiveness of the OCS Lung System. This all-comers registry is designed to evaluate the use of the OCS device in the real-world setting. As such, the PAS will collect data on all donor lungs that are preserved on the OCS system and all patients who receive OCS-treated lungs. The only exception is the transplantation of OCS-treated marginal lungs that are tracked in the EXPAND II trial. Data will be collected through the United Network of Organ Sharing (UNOS) Registry. Data that are not routinely collected in UNOS, but required for the PAS will also be collected, with source document verification.

Five hundred (500) patients who are transplanted with OCS-perfused lungs at 30 sites in the United States will be followed for 5 years post-transplantation. The primary endpoint is patient and graft survival at 12 months. The co-secondary endpoints are total ischemic time and incidence of PGD3 within 72 hours. Additional study endpoints include: PGD3 at 72 hours; total ischemia and cross-clamp times for the first and second transplanted lungs; lung graft-related serious adverse events through 30 days post-transplant or initial hospital stay (whichever is longer) including respiratory failure, bronchial anastomotic complications, and pulmonary-related infection; patient survival at 30 days; patient

survival through initial hospital stay (if longer than 30 days); Kaplan-Meir estimates for patient survival at months 1, 6, 12, 24, 36, 48, and 60; BOS-free survival at months 12, 24, 36, 48, and 60; freedom from BOS at months 12, 24, 36, 48, and 60; incidence of BOS at months 12, 24, 36, 48, and 60; re-transplantation at months 12, 24, 36, 48, and 60; and freedom from re-transplantation and mortality at months 12, 24, 36, 48, and 60.

In addition to the patient outcomes listed above, data will be collected on donor lung turn down and conversion to cold storage following OCS instrumentation. Data related to the OCS device will also be collected, including preservation and ventilation parameter trends (i.e. pulmonary artery pressure, peak airway pressure, and vascular resistance), lung oxygenation capacity, and device malfunctions.

The Primary Analysis Population will be comprised of the first 289 patients who meet the approved indication for use according to adjudication by the Clinical Events Committee (CEC). The following hypothesis tests will be conducted in the Primary Analysis Population when all 289 patients have completed 1 year of follow-up. For the primary endpoint, this study will test the hypothesis that 1-year patient and graft survival in the PAS is greater than 79%. For the co-secondary endpoints, data from the PAS (OCS treatment group) will be compared to historical control data from the INSPIRE study for the following: to test the hypothesis that mean total ischemic time is lower in the OCS versus historical control groups; and to test the hypothesis that incidence of PGD3 within 72 hours is lower in the OCS versus historical control groups. The full PAS cohort of 500 patients will continue to be followed for 5 years, for evaluation of all study endpoints using descriptive analyses.

TransMedics is required to provide reports to FDA every six months for the first two years after device approval, and annually thereafter until study completion. In addition, interim reports will be submitted for analyses of 1-year and 5-year follow-up in the Primary Analysis Population. All interim reports will include the UNOS ID and CEC-adjudicated indicator for inclusion in the Primary Analysis Population for each patient enrolled to date, cumulatively. In addition, complete line-item patient-level data will be submitted as follows: every 2 years from the date of study initiation until submission of the 1-year Primary Analysis Report; in the 1-year Primary Analysis Report; and in the Final PAS Report. PAS summary data will be posted on the PAS webpage as follows: information on study progress from each interim report limited to: number of sites enrolled; number of patients enrolled; baseline characteristics (such as age, race/ethnicity, etc); results from the 1-Year Primary Analysis Report (1-year follow-up data in the Primary Analysis Population); and results from the final PAS Report (5-year follow-up in 500 patients).

Independent third-party audits will be conducted bi-annually for the first 36 months after study initiation and annually thereafter. Audit reports will be submitted to the FDA by the independent third party auditor including any corrective action plans that are required to address the audit findings. A data safety monitoring board, steering committee, and CEC will provide additional data monitoring and study oversight for the duration of the study.

Within 30 days of receiving the Approval Order, TransMedics must submit a PMA supplement that includes the agreed upon complete protocol for the new enrollment post-approval study described above, including the electronic Case Report Forms (eCRFs). Subject enrollment in the PAS may not begin until agreement has been reached on the finalized eCRFs.

3. Labeling and training requirements.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

Christie et al. Report of the ISHLT working group on primary lung graft dysfunction: Part II. Definition. J Heart Lung Transplant 2005;24:1454–1459.

APPENDIX A. PRIMARY GRAFT DYSFUNCTION CLASSIFICATION USED IN INSPIRE TRIAL

- If a patient is intubated, PGD will be assessed primarily based on the PaO2/FiO2 ratio and chest radiograph (CXR) read out according to the 2005 ISHLT consensus statement:

International Society for Heart and Lung Transplantation Primary Graft Dysfunction

GRADING SCHEMA: (Christie, 2005)

Grade	PaO_2/FiO_2	Radiographic Infiltrates Consistent with Pulmonary Edema
0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

- If the patient is extubated, the PGD will be assessed as either 0 or 1 based on the absences or presence of infiltrates or edema on CXR respectively.
- If the patient is on post-transplant ECMO for oxygenation support, PGD will be graded as 3 automatically, except for center specific prophylactic ECMO support for patients with pulmonary hypertension or hemodynamic support and not for oxygenation.