SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Ex Vivo Lung Perfusion (EVLP)

Device Trade Name: XVIVO Perfusion System (XPS™) with STEEN Solution™ Perfusate

Device Procode: PHO

Applicant's Name/Address: XVIVO Perfusion, Inc.
3666 S. Inca Street
Englewood, CO 80110

Date of Panel Recommendation: None

Premarket Approval Application Number: P180014

Date of Notice of Approval: April 26, 2019

II. INDICATIONS FOR USE

The XVIVO Perfusion System (XPS™) with STEEN Solution™ Perfusate is indicated for use in flushing and temporary continuous normothermic machine perfusion of initially unacceptable excised donor lungs during which time the *ex vivo* function of the lungs can be reassessed for transplantation.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The Warnings and Precautions can be found in the XPS™ with STEEN Solution™ Perfusate labeling (Instructions for Use).

V. DEVICE DESCRIPTION

A. Overview of the Device System

The XPS™ with STEEN Solution™ Perfusate consists of the XPS Perfusion Cart Hardware, fluid path and non-fluid path disposables, XPS Cart Software, and STEEN Solution™. The STEEN Solution™ is a clear, sterile, non-pyrogenic, non-toxic physiological salt solution containing human serum albumin (HSA) and dextran 40. This solution is an extracellular (low potassium) electrolyte solution with physiological colloid-osmotic pressure (COP) designed for use as a temporary continuous normothermic machine perfusion solution for *ex vivo* assessment of isolated lungs after removal from the donor.

B. Device System Component Description

XPS Perfusion Cart Hardware

The XPS Perfusion Cart is designed with the sub-assembly parts shown in Figure 1.

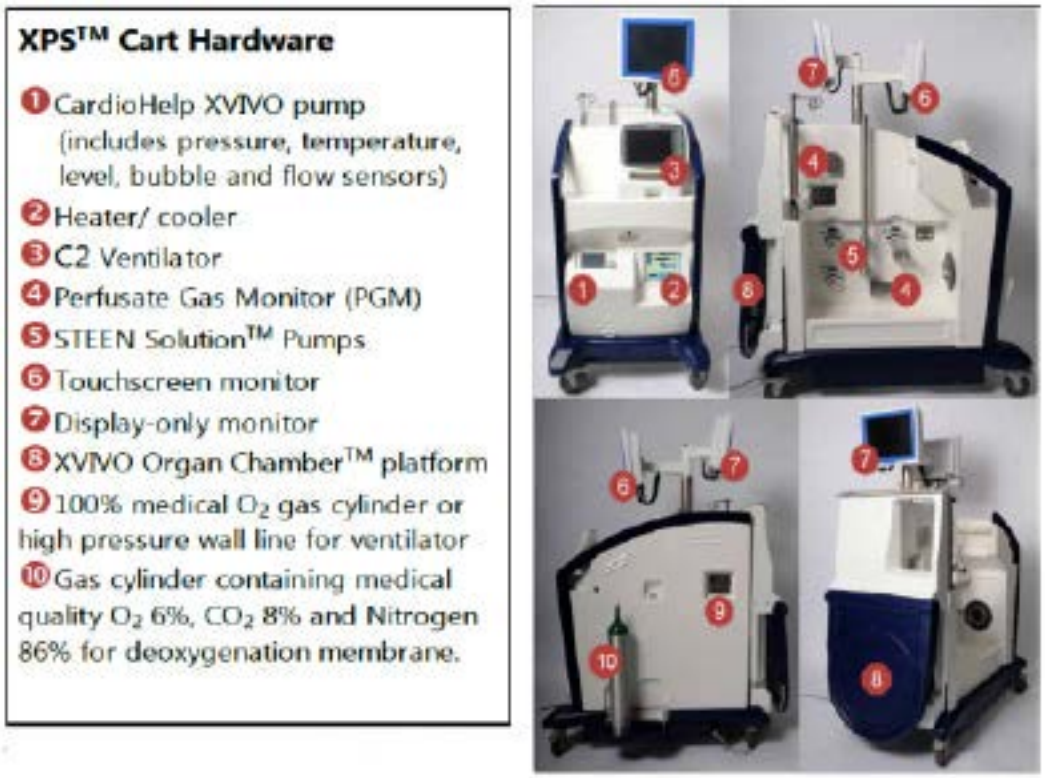


Figure 1 – XVIVO Perfusion System (XPS™)

CardioHelp XVIVO Centrifugal Pump

The CardioHelp XVIVO is a centrifugal pump with bubble, level, flow, temperature, and pressure sensors, and is identical in function to the 510(k) cleared CardioHelp System (K102726). It pumps the STEEN Solution™ into the lung(s) and monitors the temperatures and pressures going into and coming out from the *ex vivo* lung(s).

Heater/Cooler

The Hirtz VarioTherm 550 Heater/Cooler Unit (HCU) provides water at a set water temperature that flows into the medical device heat exchange interface to create the normothermic environment during EVLP. The HCU pumps water to the Quadrox-iR heat exchange membrane to control the temperature of the STEEN Solution™ perfusate through conduction. The HCU water does not come in contact with the STEEN Solution™ or any other portion of the aseptic fluid path. It remains on the non-aseptic side of the heat exchange membrane of the Quadrox-iR.

C2 Ventilator

The Hamilton C2 ventilator is an Intensive Care Unit (ICU) pressure-controlled ventilator used to ventilate the lungs during *ex vivo* perfusion and is identical to the 510(k) cleared C2 ventilator (K092148). It allows the user to pre-set pressure and volume limits according to the established EVLP ventilation protocols, preventing the C2 ventilator from over-ventilating and, therefore, damaging the *ex vivo* lung.

Perfusate Gas Monitor (PGM)

The PGM is an in-line trending monitor that measures the following critical gas parameters in the circulating STEEN Solution™: pH, PCO_2 (partial pressure of dissolved CO_2), and PO_2 (partial pressure of dissolved O_2). These parameters are displayed in real time to the operator. The PGM has no direct contact with the sterile fluid path. It uses fluorescent Light-Emitting Diodes (LED) light transmission through an in-line disposable device that contains pre-calibrated sensors.

STEEN Solution™ Peristaltic Pumps

The three (3) pumps aseptically move STEEN Solution™ to 1) fill the hard shell reservoir during priming; 2) remove it from the perfusion circuit into a connected drain bag; and 3) recycle it back to the reservoir from the XVIVO Organ Chamber™.

Monitors & Controls

- The AAEON medical grade touchscreen monitor has an integrated computer central processing unit (CPU) to connect to the XVIVO Perfusion Cart hardware for data stream transfer for display purposes. In addition, the computer Central Processing Unit (CPU) connects to the three (3) Allied Motion peristaltic pump motors to display data as well as control motor function (on/off, low/medium/high speed).
- The AAEON medical grade display-only monitor (no touch) provides data stream information to the surgeon/sterile side of the XVIVO Perfusion Cart.

Software

The XVIVO Perfusion Cart Software comprises the software system that resides on the AAEON Computer/Touchscreen Display and provides the following:

- Data stream displays from CardioHelp XVIVO, Hamilton C2 ventilator, and XVIVO PGM;
- Control and data display of Allied Motion peristaltic pump motors.

XVIVO Organ Chamber™ platform

The hinged table is attached to the sterile side of the XVIVO Perfusion Cart and locks in place in the horizontal position to provide a location to set the XVIVO

Organ Chamber™.

Gas Cylinders

The perfusion cart has two (2) gas cylinders, one containing medical grade (100%) oxygen for membrane oxygenation and the other containing a mixture of medical grade gases (6% O_2, 8% CO_2, 86% N_2) for membrane deoxygenation.

Power Distribution & Subsystem

The power subsystem assembly provides power and backup power to critical hardware items in the XVIVO Perfusion Cart. The subassembly is made up of the following:

- The UPS (uninterruptable power supply) provides battery backup support to the AAEON display and touchscreen monitors and PGMs. The CardioHelp XVIVO and the Hamilton C2 ventilator have their own internal battery backups. The Hirtz Variotherm 550 heater/cooler consumes too much power to run on battery power, so in case of emergency power outage, this device is not supported.
- The Power Supply is the Synqor +24 Volt DC power supply and is capable of supplying up to 400W of power.
- The Isolation Transformer is the Powertronix and it is used to protect equipment from power spikes and to filter out electrical interference.

Single Use Disposables

The XPS™ System interfaces with single-use disposable products, including STEEN Solution™, the XVIVO Lung Cannula Set™, the XVIVO Disposable Lung Circuit™, and the XVIVO Organ Chamber™. They are designed to interact safely and aseptically with the fluid path during EVLP.

Figure 2 – XVIVO Perfusion Disposable Components

C. Safety Elements

A number of safety elements are incorporated into the XPS with STEEN Solution Perfusate device, including:

- Audible and visual alarms indicating perfusate flow, device status, and connections to software and battery status;
- Battery for alarms in the event that both primary power and batteries fail;
- Keyed connectors for all cable, console, and disposable connections;
- 24 hour, 365 days per year technical support;
- Detailed directions for use;
- Device/system training.

All system components, with the exception of the single-use items, are intended for use on multiple *ex vivo* lungs. These components can be used for multiple *ex vivo* lungs, but only on one set of donor lungs at a time (the device can treat single and double lungs). The XPS™ with STEEN Solution™ Perfusate device is intended for

use in an aseptic setting to provide mechanical circulatory support during EVLP assessment.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the preservation of donor lungs. 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. Standard of care procedures used in the preservation of standard-criteria or ideal donor lungs typicaly consist of the cold, static storage of the lungs in a hypothermic preservation solution prior to transplantation. Normothermic machine perfusion of standard-criteria double lungs is available with the TransMedics Organ Care (OCS™) Lung System, which was approved in 2018 under P160013. Other options are not to transplant, which would mean the patient would remain on the transplant waiting list and would undergo mechanical ventilation and/or extracorporeal membrane oxygenation, if necessary. Cold, static storage is sometimes used for non-ideal lungs under practice of medicine at the discretion of the transplant surgeon.

The XVIVO XPS™ System and STEEN Solution Perfusate™ received approval as a humanitarian device under H120003 on August 12, 2014, for the normothermic flushing and assessment of previously unacceptable excised donor lungs.

VII. MARKETING HISTORY

The XVIVO Perfusion System (XPS™) and STEEN Solution Perfusate™ has been marketed in the United States (U.S.) since 2014, having gained marking approval under H120003. The STEEN Solution Perfusate™ obtained CE marking in 2006 and became available for use with commercially available cardio-pulmonary by-pass circuit equipment. Australian Therapeutic Goods Administration (TGA) approval was obtained in 2009. Hundreds of EVLP transplants using the XTS™ System and STEEN Solution™ have been performed worldwide. STEEN Solution Perfusate™ received approval by Health Canada on November 6, 2012. Including the EVLP transplants performed in the clinical trial, Toronto General Hospital has transplanted over 100 patients with EVLP lungs. The XPS™ System, XVIVO Organ Chamber™, XVIVO Lung Cannula Set™, and XVIVO Disposable Lung Circuit™ obtained their CE marking in 2014. In addition, these devices are commercially available and marketed in Australia and Canada.

None of these devices have been withdrawn from marketing for any reasons related to the saftety and effectiveness of these devices.

Several device changes have been implemented since the approval of the H120003 in August of 2014. These are summarized in the table below.

Table 1 – Device Modifications Since 2014

Device Modification Description	HDE Supplement	FDA Decision and Date
Device Modification (Software Changes)	H120003/S001	Approval; 11/10/2014
Device Modification (Hardware Changes)	H120003/S002	Approval; 11/10/2014
STEEN Manufacturing Site Change	H120003/S003	Approval; 6/2/2015
Labeling Change (Revision K of Operator's Manual)	H120003/S005	Approval; 11/16/15
Filter Change	H120003/S006	Approval; 11/13/15
Software Modification (Version 3.3 of XPS™ System)	H120003/S007	Approval; 1/7/2016
Software Modification (Version 4.0 of XPS™ System)	H120003/S008	Approval; 11/16/2016
Change in Sterilization Site	H120003/S009	Acknowledgement; 12/12/18

As can be seen, these changes were submitted to FDA for review and received approval.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The XPS™ with STEEN Solution™ Perfusate device is indicated for use only on previously unacceptable excised donor lungs in an *ex vivo* setting. There is no direct patient contact when this device is used as labeled; however, the device has a direct contact with the lungs that are subsequently transplanted into the recipients. The donor lung quality and optimization after preservation have direct effects on allograft function and survival.

The potential for contamination and mechanical trauma, due to the manipulation and cannulation of the lung airway and vascular structures, may lead to complications after transplantation.

Patients receiving a lung treated with the XPS™ System with STEEN Solution™ Perfusate device may experience adverse events including those experienced with any lung transplant.

Below is a list of the potential adverse effects associated with the use of the device.

- Death
- Renal failure or dysfunction
- Respiratory dysfunction or failure
- Respiratory infection
- Sepsis

- Primary graft dysfunction
- Acute or chronic rejection
- Cardiac arrhythmias
- Bronchiolitis Obliterans Syndrome (BOS)
- Bronchial stenosis/Dehiscence

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

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

The bench testing consisted of performance, safety and reliability testing.

1. *Biocompatibility*

Biocompatibility testing of the XPS™ disposables and STEEN Solution™ was performed in accordance with the FDA Blue Book Memorandum #G95-1 and Biological Evaluation of Medical Devices Guidance - International Standard ISO 10993-1, and in accordance with United States Pharmacopoeia – XXIII. The specific tests included: cytotoxicity, sensitization, intracutaneous irritation, systemic toxicity, hemocompatibility, endotoxin, and sub-chronic toxicity.

a. STEEN Solution™

Biocompatibility testing according to ISO 10993, Part 1, was performed on STEEN Solution™. The results showing it is a biocompatible product are provided in Table 2.

Table 2 - STEEN Solution™ Biocompatibility Matrix

Experimental Study	Results
Cytotoxicity study using the ISO agarose overlay method, liquid-macroscopic and microscopic evaluation of mouse fibroblast cell culture.	STEEN Solution™ showed no evidence of causing cell lysis or toxicity and conforms to the relevant sections of ISO 10993: Biological evaluation of medical devices part 5: Test for cytotoxicity *In Vitro* Method.
ISO modified intracutaneous study of the rabbit modified for a chemical solution.	STEEN Solution™, injected intracutaneously into rabbits, showed no evidence of causing significant irritation and conforms to relevant sections of ISO 10993: Biological evaluation of medical devices part 10: Tests for Irritation and Sensitization- modified for chemical solutions.

Experimental Study	Results
Acute systemic toxicity study following IV dose range finding/ limit dose study in the mouse.	STEEN Solution™ showed no evidence of mortality or significant systemic toxicity and conforms to relevant sections of ISO 10993: Biological evaluation of medical devices part 11: Tests for Systemic Toxicity.
Murine local lymph node assay by topically dosing the dorsum of the mouse ear.	STEEN Solution™ was not considered to be sensitizing to the mouse and conforms to relevant sections of ISO 10993: Biological evaluation of medical devices part 10: Tests for Irritation and Sensitization- modified for chemical solutions.
In vitro hemolysis study (modified ASTM-direct contact method) of diluted rabbit blood.	STEEN Solution was nonhemolytic and conforms to relevant sections of ISO 10993: Biological evaluation of medical devices part 4: Selection of Tests for Interactions with Blood.
White blood cell *in vitro* morphology study of anticoagulated whole canine blood.	STEEN Solution™ did not have an effect upon white blood cell morphology and conforms to relevant sections of ISO 10993: Biological evaluation of medical devices part 4: Selection of Tests for Interactions with Blood.
In Vitro Lee-White clotting time study of canine blood.	STEEN Solution appeared to have no effect on clotting time according to the study and conforms to relevant sections of ISO 10993: Biological evaluation of medical devices part 4: Selection of Tests for Interactions with Blood.

b. XVIVO Organ Chamber™ XVIVO Lung Cannula Set™, XVIVO Disposable Lung Circuit™, and XVIVO Disposable PGM Sensors™

Each of these devices was extracted and tested under Good Laboratory Practices (GLP) conditions in accordance with ISO 10993 standards, showing all materials are biocompatible, as listed in the Table 3, below.

Table 3 - XVIVO Disposables Plastics Biocompatibility Matrix

Subject	Standard/Method	Pass/Fail
Cytotoxicity	MEM Elution, ISO 10993-5	Pass
Sensitization	Murine Local Lymph Node Assay (LLNA), ISO 10993-12	Pass
ISO Intracutaneous Reactivity/ Toxicity	Albino rabbits, intracutaneous injections, ISO 10993-10	Pass
Systemic Toxicity	Material Mediated Pyrogen, ISO 10993-11	Pass

Subject	Standard/Method	Pass/Fail
Sub-chronic Toxicity	Systemic Injection, ISO 10993-11	Pass
Hemocompatibility	ASTM Hemolysis, ISO 10993-12, ISO 10993-4	Pass
Endotoxin	LAL Test, USP <85> ANSI/AAMI ST72:2002	Pass

2. *Sterilization Validation*

   a. STEEN Solution™

      The STEEN Solution™ is provided sterile to the user. The device is sterilized via aseptic filtration using a 0.20µm filter into sterile Nalgene bottles. The sterilization method was validated to ensure successful sterilization to a Sterility Assurance Level (SAL) of 10^{-3} in accordance with USP 32 <71> Sterility Tests (method for Membrane Filtration).

   b. XVIVO Organ Chamber™, XVIVO Lung Cannula Set™, and XVIVO Disposable Lung Circuit™

      These components are also provided sterile to the user. These devices were extracted and tested under GLP conditions in accordance with the American National Standards Institute, Inc. (ANSI) standard ANSI/AAMI/ISO 11135 (Medical Devices - Validation and Routine Control of Ethylene Oxide Sterilization). All tests passed and the products were sterilized by the validated SAL 10^{-6} ethylene oxide sterilization cycle.

3. *Hemolysis Testing*

   STEEN Solution™ is an acellular (no red blood cells) perfusate and is used without adding blood to the perfusion circuit, minimizing any risk of hemolysis. The centrifugal pump head used during EVLP (MAQUET Rotaflow) has previously been shown (K991864) to minimize hemolysis and is comparable to other centrifugal pump devices marketed for use with blood products.

4. *Software Verification and Validation*

   Software on-board the XPS™ Perfusion Cart was verified and validated in accordance with the FDA Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices. The software is of major level of concern, since the viability of the donor lungs will be impacted, should device/software malfunctions occur. The software information and validation included a description of the software architecture, a Product Requirements Document, Design Specification document, Verification Protocol, Validation Protocol, Hazard Analysis and Risk Assessment Summary, Traceability Matrix,

Revision Level History, list of unresolved anomalies (bugs), compatibility testing between the various components of the XPS™ System, testing of alarms and alarm conditions and overall validation of device functionality.

5. *Shelf Life Studies*

   A combination of real-time aging (STEEN Solution™, XVIVO Lung Disposable Circuit™) and accelerated aging studies (XVIVO Organ Chamber™, XVIVO Lung Cannula Set™) were performed in accordance with ASTM F1980. These studies demonstrated that sterility, package integrity, and product functionality could be maintained as follows:

   - STEEN Solution™: 2 years
   - XVIVO Disposable Lung Circuit™: 2 years
   - XVIVO Organ Chamber™: 4 years
   - XVIVO Disposable Lung Cannula Set™: 4 years

6. *Electrical Safety Testing*

   An independent laboratory has evaluated the electrical safety of the XPS™ device. The test results demonstrate that the XPS™ System meets the applicable requirements of IEC 60601-1, the European standard for general safety requirements for medical electrical equipment, as summarized in Table 4.

Table 4 - Electrical Safety Testing Summary

Standards and Approvals	
IEC 60601-1-1	Medical electrical equipment – Part 1: General requirements for basic safety and essential performance Collateral Standard: Safety requirements for medical electrical systems
IEC 60601-1-2	Medical electrical equipment – Part 1-2: Collateral Standard: Electromagnetic compatibility-Requirements and tests
IEC 60601-1-4	Medical electrical equipment – Part 1-4: Collateral standard: Programmable electrical medical systems – Evidence checklist
IEC 60601-1-8	Medical electrical equipment – Part 1-8: Collateral standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems
EN 1041	Information supplied by the manufacturer with medical devices
EN 980	Graphical symbols for use in the labeling of medical devices

Standards and Approvals	
ISO 15223	Medical devices symbols to be used with medical device labels, labeling and information to be supplied

7. *Electromagnetic Compatibility (EMC) Testing*

   The XPS™ System was tested by an independent laboratory to demonstrate that it meets the requirements for conducted and radiated emissions, electrostatic discharge immunity, radiated electromagnetic immunity, electrical fast transient/burst immunity, and conducted disturbance induced by radio frequency fields. The test results demonstrated that the XPS™ System meets the applicable requirements of the 2001 version of IEC 60601-1-1-2, the standard for electromagnetic capability (EMC) for medical electrical equipment.

8. *System Reliability*

   The reliability of the main components of the XPS™ System has been shown via the individual component manufacturers' data from the specific products, which are 510(k) cleared and CE marked. The main components are the following:

   - CardioHelp pump (K102726, CE Marked)
   - C2 Ventilator (K092148, CE Marked)
   - Variotherm Heater/Cooler (CE Marked)

B. <u>Animal Studies</u>

1. Animal and Rejected Human Lung Testing

   Three (3) porcine lungs and one (1) rejected human lung were perfused using the XPS™ System with STEEN Solution™ Perfusate on distinct dates under the direction of different transplant surgeons. Each perfusion was done under controlled conditions, using the procedure outlined in the Vitrolife/XVIVO "NOVEL LUNG TRIAL- Normothermic Ex Vivo Lung Perfusion (EVLP) as an Assessment of Extended/Marginal Donor Lungs (Protocol number VSS-NA-001)." The lungs were removed from the donor following standard lung recovery procedures (e.g., hypothermic flush with Perfadex® and placed in cold (ice) storage during transportation). Upon arrival at the test site, the lungs were removed from the hypothermic container and placed in a sterile basin for temporary storage. The straight pulmonary artery (PA) cannula from the XVIVO Lung Cannula Pack™ was selected and attached to the PA using umbilical tape to secure the cannula in place. The cone-shaped left atrial (LA) cannula was selected to connect the LA using a 4.0 running monofilament suture to provide effective connection for reliable outflow drainage. The perfusion tubing from the MAQUET disposable lung circuit was connected to the lungs using straight 3/8" hose connectors. The shape and size of the cannulas were designed to safely hold open the pulmonary artery and left atrial cuff to allow the fluid to move smoothly through the lung and to monitor the

pressures in the lung, while visualizing the flow of the solution. Extracorporeal circulation (i.e., flow) was provided by the XPS™ System. Table 5 provides data obtained from the XPS™ software indicating that the various components of the XPS™ system were functioning properly.

Table 5 - Pre-Clinical Results

DATE	Test Subject	CardioHelp Pump	C2 Ventilator	Variotherm HCU	PGM Sensors
9/3/10	Porcine	Pass	Pass	Pass	Pass
9/4/10	Porcine	Pass	Pass	Pass	Pass
10/26/10	Porcine	Pass	Pass	Pass	Pass
12/6/10	Human	Pass	Pass	Pass	Pass

The results of the four (4) laboratory tests (three (3) porcine and one (1) human lung) show that the XPS™ ventilator, pump (and associated disposables including deoxygenator membrane), and PGM worked safely and efficiently together during both animal (pig) and human lung perfusion tests and similarly to what was expected based on the published (and unpublished) data from the University Health Network, Toronto group during its human ex vivo lung perfusion ("HELP") clinical trial. The XVIVO Disposable Lung Circuit™ built by MAQUET Cardiopulmonary AG perfused both pig and human donor lungs in the XPS™ System using the STEEN Solution™ Perfusate efficiently and safely with results within normal expected ranges.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

Data from two (2) clinical trials, the HELP Trial and the NOVEL Trial, were considered to support H120003 for the safety and probable benefit of EVLP when used to reassess initially unacceptable donor lungs perfused at near normal body temperature (normothermia) in an *ex vivo* setting. Both trials were sponsored by Vitrolife, Inc., which became XVIVO Perfusion, Inc., in late 2012.

Table 6 - Supporting Clinical Studies

	EVLP-Transplanted	Cold Storage (Control)
HELP Trial (Canadian Trial)*: Normothermic EVLP for an Improved Assessment of Donor Lungs for Transplantation	n= 50	n= 253
NOVEL and NOVEL Extension Trials (U.S. Trials): Normothermic EVLP as an Assessment of Extended/Marginal Donor Lungs	n= 110	n= 116

* Cypel M., et al., 2012

In the earlier Canadian Trial (HELP Study, 2008-2010, Toronto), STEEN Solution™ was perfused with available off-the-shelf equipment. This hardware and single-use disposable equipment set was functionally equivalent to the subsequent components of the XPS™ System and, in fact, provided a basis for the development of the XPS™ System. This study was not powered to show statistically significant differences in the predefined endpoints. A brief summary of the HELP Trial appears below.

Data from the U.S. clinical trial (NOVEL Trial, 2011-2013) were considered as the pivotal data to support the safety and probable benefit of EVLP using the XPS™ System with STEEN Solution™ Perfusate for H120003. The NOVEL study was expanded after the approval of the HDE application and the full cohort, comprised of the NOVEL (2011-2014) and the NOVEL Extension (2014-2017) studies, was the basis for the PMA approval decision. A summary of the NOVEL and NOVEL Extension is presented in subsection 2.A, below.

1. Canadian HELP Study (N=22, plus an additional compassionate use extension of 39, for a total N=61)

HELP Trial Study Design

The HELP study was a prospective, non-randomized, single-center study that reviewed clinical outcomes between initially rejected donor lungs treated with four (4) hours of EVLP using STEEN Solution™ (study group) and all other lung transplants performed during the same study period and preserved using standard static cold storage (CS) methods with Perfadex™ Preservation Solution (Control Group).

Initially rejected lungs were defined as those not meeting the clinical donor lung criteria, based on the 2003 International Society of Heart and Lung Transplantation (ISHLT) consensus document on lung transplant acceptability criteria (Orens et al., 2003).

After four (4) hours of EVLP perfusion, the donor lung was evaluated for a delta PO_2 > 350mmHg and stable pulmonary vascular resistance (PVR), peak airway pressure, and lung compliance (i.e., < 15% deterioration). If meeting these transplantability criteria, the donor lungs were considered acceptable for transplantation.

During the initial phase, this study included three (3) standard criteria lung transplants in a safety pilot study. In addition, the study included 19 initially unacceptable lung donors for transplantation. A subsequent compassionate use extension arm was added to the study, increasing the sample size with 39 additional patients for a total of 61. Data from the study were reported to FDA at various stages of the HELP study, as they became available during the review of H120003, and were also published by different authors at different times, thus the sample sizes in the various analyses are not consistent, as seen in the tables below. All the included donor lungs were transplanted after EVLP normothermic preservation.

Donor/recipient selection was based on first available lungs that did not meet the

criteria for standard, "ideal" donor lung (Orens et al., 2003, if not 'standard,' proceed through EVLP), and recipient match.

A study design limitation, which resulted from ethical considerations, was the inability to randomize the initially rejected donor lungs to 'EVLP' or static cold storage.

The study's primary endpoint was the incidence of primary graft dysfunction (PGD) Grades 2 and 3 at 72 hours after transplantation. The study was not powered to demonstrate statistical differences across study groups for the endpoints.

HELP Trial Results

Primary Graft Dysfunction Grades

The primary endpoint in the study (e.g., incidence of PGD Grades 2 and 3 at 72 hours after transplantation) showed that the EVLP recipient group had no significant difference in comparison to those in the Control Group. PGD Grade 2 at 72 hours was 11% and 23% in the EVLP and Control Arms, respectively, while PGD Grade 3 at 72 hours was 3% and 11% in the EVLP and Control Arms, respectively (see Table 7). Similarly, Cypel et al., 2012, reported that PGD Grade 3 at 72 hours was 2% and 8.5% in the EVLP and control arms, respectively (see Table 8).

Table 7 - PGD Grades, HELP Trial

Toronto General Hospital Patients - PGD						
PGD Grade	**Controls N=103**			**EVLP N=35**		
	T 0 hr	T 24 hrs	T 72hrs	T 0hr	T 24hrs	T 72hrs
1	72	55	63 (61%)	25	28	30 (86%)
2	16	33	24 (23%)	5	5	4 (11%)
3	15	9	11 (11%)	5	2	1 (3%)
No value obtained	0	6	5	0	0	0

Note: Extubated patients were not given a PGD score

Table 8 - Recipient Outcomes in ex vivo Lung Perfusion, HELP Trial

Variable	EVLP (n=50)	Controls (n=253)	P value
PGD 3 at 72h (%)	2	8.5	0.14
ECLS (%)	2	2.7	1.00
Mechanical ventilation (d)			0.30
Median	2	2.2	
Range	1-101	1-43	
ICU stay (d)			0.32
Median	4	4.5	
Range	1-100	1-257	
Hospital stay (d)			0.11
Median	20	23	
Range	7-156	1-299	
30-d mortality (%)	4	3.5	1.00
Anastomotic stricture requiring intervention (%)	4	4	1.00

EVLP, Ex vivo lung perfusion; PGD, primary graft dysfunction; ECLS, extracorporeal life support; ICU, intensve care unit

Source: Table obtained from Cypel *et. al*., 2012, includes "compassionate extension."

Controls: Standard static cold storage.

Survival Analyses

Thirty-day mortality was reported as 4% and 3.5% for the EVLP and control arms, respectively (p=1.0). Table 9 below presents survival data at 1, 2, and 3 years post-transplant.

Survival at 3 years was comparable across arms, 67% (n=28) versus 71.2% (n=163) for the EVLP and control arms, respectively. The early deaths in the study group were attributed to postoperative complications (i.e., retroperitoneal bleeding and sepsis). It was concluded that these complications "were not directly related to the allograft."

It should be noted that the total number of recipients in the HELP trial's EVLP arm was 61, but at 3 years, only 28 were included in the survival analysis. The status of the remaining 33 patients is unknown (see Table 9). Finally, since the data were obtained from the Applicant's HDE application (H120003), as well as from the cited publications, there are some discrepancies in the patient numbers, since different analyses included different sample sizes.

Table 9 - HELP Study Survival Outcomes and Highest Predicted FEV1 Data

	EVLP	N	Control	N	Significance
Survival 1 year	83.7%	49	85.1%	262	P=0.83 (F)
Survival 2 years	75.0%	44	78.4%	236	P=0.69 (F)
Survival 3 years	67.9%	28	71.2%	163	P=0.82 (F)
Number of acute rejections/year	0.54±0.72	39	0.47±0.65	204	P=0.54 (MW)
Highest Predicted FEV1 (only double lungs)	73.5%±28%	35	71.8%±25%	220	P=0.67 (ST)

F=Fisher's exact test; MW=Mann-Whitney; ST=Student's T-test.

The updated survival data from Toronto General Hospital is listed in Table 10 below.

Table 10 - HELP Survival (last follow up – May 24, 2013*)

Toronto General Hospital Patients-Survival		
	Control (N=397)	**EVLP (N=74)**
Alive	309 (78%)	57 (77%)
Expired	88 (22%)	17 (23%)
Survival Day (Range)	Mean 687 (1-1709) Median 597	Mean 629 (7-1702) Median 531

* The HELP trial was conducted at the Toronto General Hospital, University of Toronto, Canada, from September 25, 2008 to February 28, 2010, and the results from this study were published in Cypel et al., 2010. The HELP Study included 22 lung transplant recipients of EVLP lungs during its "initial phase," and subsequently added 39 more transplanted patients during the "compassionate extension phase" of the study. The update on this study was published by Cypel et.al., 2012.

Allograft Function Analyses

Pulmonary function test (PFT) data over time were not available, limiting FDA's ability to draw valid conclusions. The prospective collection of PFT data was not part of the original HELP study protocol. The limited data available for H120003 included only the highest predicted FEV1 (%) on double lung transplants (Table 9).

2. NOVEL and NOVEL Extension Study

A. Study Design

The main clinical study used in support this PMA application was the NOVEL study, including its NOVEL Extension portion. The NOVEL study is the Applicant's original clinical study for the XPS™ System, dating back to the approval of the original IDE (G100104) in March of 2011. A cohort from that study was used in the approval of the Applicant's HDE H120003. Upon the approval of the HDE in August of 2014, FDA and the Applicant worked to modify and expand the NOVEL clinical protocol to collect data for this PMA, as well as to satisfy the post-approval study (PAS) requirements of the HDE approval. As such, the study was expanded to encompass 220 subjects (110 in each arm), which would be the cohort used for the PMA application, and 20 investigational sites. This PMA cohort would include the 62 subjects (31 in each arm) that had already been submitted in H120003. In this PMA application, the Applicant has designated the study prior to these modifications and expansions the "NOVEL study," while the portion after the modifications were implemented has been designated the "NOVEL Extension study."

The study remained as a controlled, non-randomized study with the Control Arm being standard-criteria lungs stored and transported with standard-of-care (SOC), cold, static, preservation solution. The Control lungs were contemporaneous to the EVLP lungs and were transplanted at the same centers as those from the EVLP arm. The timeframe of the study was through the first year after transplantation, although the HDE's PAS, which was built into the same protocol as the NOVEL study, followed patients to 3 years post-transplantation.

Other modifications included in the NOVEL study protocol at the time of H120003 approval included changes in the primary endpoints, changes in the definitions and categorization of adverse events, changes in the follow-up period (follow-up was increased to three years post-transplantation), some changes in the study entry criteria, and some changes in the acceptability criteria for EVLP, as well as the transplantability criteria post-EVLP. These protocol changes were largely informed by the HDE application and discussions held at the GU Advisory Panel meeting for the HDE.

Additionally, there were 16 more subjects per arm that were enrolled for the purposes of the HDE's PAS. In total, the PAS would encompass 252 subjects, 126 in each arm.

Patients in the NOVEL and NOVEL Extension were treated between 2011 and 2017. The database for this PMA reflected data collected through July 2018 and included 226 patients, in addition to the 16 HDE PAS subjects. There were 17 investigational sites that participated in the study.

The study evaluated the EVLP treatment with the XPS™ system of double and single lungs. In some cases, double lungs were instrumented in the system and

treated, but were then split and transplanted in different recipients. As such, a total of 332 donor grafts, single or double, were enrolled into the study, resulting in 110 transplanted recipients, 106 EVLP-treated donor lungs that were deemed not transplantable after EVLP, and 116 transplanted control recipients. Eleven (11) donor double lungs were split resulting in 22 single-lung recipients.

Also, it is important to reiterate that the study focused on the treatment of previously unsuitable or rejected donor lungs, considered to be non-ideal, marginal or extended-criteria. Control lungs were standard-criteria donor lungs that were transported and preserved with cold, static storage.

Once accepted for EVLP, the donor lungs would be flushed with cold preservation solution (Perfadex), packaged according to industry standards, and transported on ice to the recipient/transplant center. The XPS™ System resides at the transplant site and does not travel with the donor lungs; therefore, the donor lungs must first travel on ice and then undergo EVLP once they reach the transplant site.

Once received by the transplant site, the lungs would be unpacked, the EVLP cannula would be sutured to the left atrial cuff and pulmonary artery, and the lungs would then be placed on the XPS™ system to begin the EVLP treatment. The EVLP treatment includes antegrade perfusion to remove any clots that might have formed in the pulmonary artery during transport. Graft preparation time is measured from the time of unpacking to the start of antegrade perfusion. The lungs would be warmed and perfused on the EVLP circuit for a minimum of 3 hours and a maximum of 6 hours. Physiological parameters would be collected every hour and x-rays would be taken at 1 hour and possibly later in the EVLP period, if requested by the transplant team. The x-ray provides secondary confirmation of improvement if the reason for initial rejection was pulmonary edema. Edema could also be evaluated by the surgeon (e.g., by lifting the lung to determine whether it has become less boggy and heavy, or by visually inspecting the frothing coming from the lung).

After EVLP, the lungs would be assessed for transplantability and deemed acceptable for transplantation or not. If accepted for transplantation, the lungs would be taken off of the XPS™ System, cooled and placed back on ice in the standard, sterile method used for organ storage. According to the Applicant, this second cooling period is necessary to decrease the chance of lung degradation during the implantation procedure.

1. Clinical Inclusion and Exclusion Criteria

   The following pre-EVLP eligibility criteria were to be followed for donor lungs:

   The donor lung must meet the following inclusion criteria to proceed with EVLP:

   - $PaO_2/FiO_2 \leq 300$ mmHg at the time of clinical evaluation, OR

- If PaO2/FiO2 > 300mmHg, the donor must have one or more of the following risk factors:
  - Multiple blood transfusions (> 10)
  - Pulmonary edema detected via chest x-ray, bronchoscopy or palpation of lungs.
  - Donation after circulatory death (DCD).
  - Investigator evaluation of the donor lung as "unsuitable" for transplant.

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

- Significant active pneumonia and/or persistent purulent secretions on bronchoscopy or as determined by investigator.
- Known significant aspiration of gastric contents within the lung.
- Significant mechanical lung injury or trauma determined by chest x-ray, bronchoscopy, CT scan or visual inspection.
- Active infectious disease such as HIV, hepatitis B or C, or syphilis. (If infectious disease information is not available at the start of EVLP, this criterion can be assessed during or after EVLP but prior to transplant.)

The following post-EVLP transplantability criteria were used in order to proceed to transplant:

- Surgeon must be clinically satisfied with the lung evaluation.
- Stability or improvement in all lung function parameters (PVR, compliance, airway pressure) during perfusion.
- $\Delta PO2 \geq 350$ mmHg at two time points during EVLP.

If two (2) $\Delta PO2 \geq 350$ mmHg could not be obtained, adaptive eligibility criteria could be used. At least three (3) of the four (4) following criteria would need to be met:

- One $\Delta PO2 \geq 350$ mmHg or absolute $PO2 \geq 400$ mmHg.
- Chest x-ray findings with absence or improvement of pulmonary edema/infiltrates.
- Static compliance > 35 for a single lung or > 60 for double lungs.
- Absence of consolidation by palpation.

The adaptive eligibility criteria were introduced in the NOVEL Extension portion of the study in 2014 after the HDE's approval.

The donor lung would be excluded from transplant if any of the following criteria were met:

- All $\Delta PO2s < 350$ mmHg (measured with FiO2 set at 1.0) or all absolute PO2s are < 400 mmHg.

- Greater than 10-15% overall deterioration of lung function across all parameters (PVR, compliance, airway pressure) with chest x-ray findings showing deterioration.
- Donor lung is positive for infectious diseases such as HIV, hepatitis B or C, or syphilis.

Regarding the recipients, the protocol included the following recipient inclusion and exclusion criteria:

A recipient may enroll in the study if they meet the following inclusion criteria:

- Requires single or bilateral lung transplant.
- Male or female, 18 years of age or older.
- Subject or subject's representative provides a legally effective informed consent.

A recipient may not enroll in the study if they meet any of the following criteria:

- Recipient is HIV positive.
- Recipient has active Hepatitis.
- Investigator believes that the recipient has another infection that excludes them from transplant in the study.
- Recipient is to receive a multi-organ transplant.
- Recipient is on hemodialysis or has chronic severe renal dysfunction (severe renal dysfunction is defined as a glomerular filtration rate of 29 mL/min/1.73m^2 or less).
- Recipient is to have planned concurrent cardiac procedures.
- Recipient is a re-transplant (re-transplant is defined as a recipient having the removal and transplant of a previously transplanted lung. A recipient with a previously single lung transplant is eligible to enroll in the trial if it is for the other lung and within 6 months of previous transplant).
- Recipient is on Nova Lung, ECMO, or other invasive mechanical ventilation at time of transplant (Continuous Positive Airway Pressure (CPAP) and Bilevel Positive Airway Pressure (BIPAP) are not exclusionary).

2. Follow-up Schedule

All patients were followed through the pre-operative and peri-operative periods, as well as post-tranplantation. Post-transplantation, patients were evaluated on Day 7, Day 30, at hospital discharge, and at 12 months post-transplantation. Additionally, through the H120003 PAS, they were evaluated for survival, lung function, adverse events and lung-related complications, such as Bronchiolitis Obleterans Syndrome (BOS), at 2 and 3 years post-transplantation.

Preoperatively, the donor lungs were screened for their EVLP assessment. The following data were collected:

- Gender;
- Age;
- Donor type;
- Cause of death;
- PaO2/FiO2;
- Cytomegalovirus;
- Smoking history;
- Analysis of x-ray;
- Secretions, if any;
- Endobronchial assessment;
- Results of sputum gram stain, if available;
- Confirmation of lung eligibility, per the approved protocol.

During EVLP, the following parameters were collected:

- Preservation information (e.g., start and stop times of EVLP procedure, start and stop times of cold preservation, volume of preservation solution used, type of preservation used, macroscopic lung evaluation);
- Ex vivo data and x-rays (i.e., x-rays at 1 hour and 3 hours, if necessary, during EVLP);
- Post-EVLP assessment (according to pre-specified criteria);
- Confirmation of lung eligibility post-EVLP (according to pre-specified criteria).

Post-operatively, for the time up to 72 hours post-transplantation, the following data were collected:

- Post-transplant lung status evaluations at 0, 24, and 72 hours;
- PGD scoring;
- Adverse events.

At Day 7, the following data were collected:

- Adverse events;
- Intubation status (including re-intubation and length of time of intubation);
- ICU status (including re-admissions);
- Hospitalization status (including re-admissions);
- Ventilator and ECMO status.

At Day 30, the following data were collected (could be collected in patient visit or via phone):

- Survival status (primary cause of death, if applicable);
- Ventilator and ECMO status;
- Adverse events;
- Assess re-admission status.

At hospital discharge, the following data were collected:

- Date of discharge;
- Amount of oxygen the patient was on at discharge;
- Length of stay in hospital (i.e., from date of transplant to date of discharge).

At the 12-month post-transplantation point, the following data were collected:

- Survival status (primary cause of death, if applicable);
- Safety assessments (e.g., graft function);
- Adverse events.

For the H120003 PAS, the following data were collected at 2 and 3 years post-transplantation:

- Survival status (primary cause of death, if applicable);
- Re-transplantations;
- Hospitalizations (including for reasons of infections);
- Evidence of noncompliance;
- Graft status (i.e., functioning or non-functioning, and if failed, reason(s) for failure or rejection);
- Graft function;
- Lung function (FEV1, oxygen requirement at rest, BOS evaluation and evaluation for bronchial strictures);
- Adverse events.

Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

Regarding safety and effectiveness, the co-primary endpoints were:

- 1-yearSurvival;
- Rate of Grade 3 primary graft dysfunction (PGD) at 72 hours post-transplant.

With regard to success/failure criteria, the clinical protocol specified that success would only be met if both the comparisons between survival rates and rates of PGD Grade 3 between the Treatment and Control Arms were successful. The null hypothesis was that the Treatment Arm was non-inferior to the Control Arm for each of the co-primary endpoints. A non-inferiority margin of 12% was specified. The primary endpoints would be evaluated using a 2-sided 95% (adjusted Wald) confidence interval. If the upper confidence limits for each of the difference in rates is no more than 0.12, then the EVLP Group would be considered non-inferior to the Control Group. The protocol specified that "accidental deaths (e.g., automobile accident)" would be excluded from the survival analysis.

The secondary endpoints were:

- Pulmonary function tests (FEV1) at 3, 6, 9, and 12 months;
- PGD scores at 24 and 48 hours post-transplantation;
- Intensive care unit (ICU) length of stay;
- Hospital length of stay;
- Post-transplantation use of extracorporeal membrane oxygenation (ECMO) due to lung function issues;
- Duration of post-transplantation mechanical ventilation;
- Quality of life and functional status at 1 year post-transplantation.

B. Accountability of PMA Cohort

At the time of database lock, of 226 patients (recipients) enrolled in the PMA study, 226 patients (100%) were available for analysis at the completion of the study (the 12-month post-transplantation visit), and could be determined to be dead or alive at that time point. There were no patients lost to follow-up in this period.

Regarding donor lungs, a total of 332 unique donor lungs were enrolled in the NOVEL/NOVEL Extension study, including 116 standard criteria, control donor lungs. Of the 216 donor lungs entered into the EVLP Group, there were 177 double lungs and 39 single lungs. Of the 177 double lungs, 89 were not transplanted after EVLP and 88 were accepted for transplantation. Of these 88 double lungs accepted for transplantation, 63 were transplanted as double lungs into 63 recipients, 11 were split and one of the split lungs was transplanted as a single lung into 11 recipients (the other lung was deemed unsuitable for transplantation after EVLP), and 7 were transplanted as single lungs into 14 recipients (split lungs where both sides were used). Of the 39 single lungs treated with EVLP, 17 were not transplanted and 22 were transplanted into 22 recipients. In all, a total of 110 recipients were transplanted with EVLP-treated lungs and 106 donor lungs were discarded after EVLP.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a transplant study performed in the U.S. The donor and recipient characteristics for the subjects included in the study are summarized in Table 11, below.

The UNOS control was used for post-hoc comparisons to the EVLP Arm. This group was comprised of transplant recipients from the same centers as those involved in the NOVEL/NOVEL Extension study, but excluding the following subjects:

- EVLP subjects
- Pediatric subjects (recipients <18)
- Ventilator use at time of transplant
- ECMO at time of transplant
- History of HIV
- Multi-organ transplant
- Re-transplant

Table 11 – Donor Demographics

Donors	NOVEL EVLP Not Transplanted N=106	NOVEL EVLP Transplanted N=110	NOVEL Control Transplanted N=116	UNOS Control Transplanted N=4898
Donor Lung Type				
Bilateral Lungs	89 84.0%	88 80.0%	85 73.3%	Data not available from UNOS
Single Lung	17 16.0%	22 20.0%	31 26.7%	
Donor Gender				
Female	34 32.1%	30 27.3%	45 38.8%	1917 39.1%
Male	72 67.9%	80 72.7%	71 61.2%	2981 60.9%
Donor Type				
Brain Dead	66 62.3%	82 74.5%	115 99.1%	4790 97.8%
Donation After Circ Death	40 37.7%	28 25.5%	1 0.9%	108 2.2%
Donor CMV				
Negative	40 37.7%	54 49.1%	50 43.1%	1899 38.8%
Positive	64 60.4%	56 50.9%	66 56.9%	2991 61.1%
Unknown	2 1.9%	0 0.0%	0 0%	8 0.2%
Cause of Death				
Trauma	43 40.6%	42 38.2%	45 38.8%	1114 22.7%
CVA	28 26.4%	25 22.7%	27 23.3%	2097 42.8%
Hypoxia	30 28.3%	36 32.7%	37 31.9%	1553 31.7%
Other	5 4.7%	7 6.4%	7 6.0%	134 2.7%
Smoking Status				
Never	45 42.5%	49 44.5%	59 50.9%	Data not available from UNOS
Current	42 39.6%	43 39.1%	36 31/0%	
Former	10 9.4%	14 12.7%	11 9.5%	
Unknown	9 8.5%	4 3.6%	10 8.6%	

Table 12 –NOVEL EVLP Donor Characteristics (before EVLP)

Donor PaO2	NOVEL EVLP			
	Not Transplanted N=106		Transplanted N=110	
PaO2 < 300	31	29.3%	40	36.4%
PaO2 ≥ 300	75	70.7%	70	63.6%

Table 13 – Marginal Reasons (for all donor lungs with PaO2 ≥ 300)

Marginal Reason	Count	Share of Responses	Rate per Case
> 10 Blood Tranfusions	18	0.0726	0.124
Pulmonary Edema	82	0.3306	0.566
DCD Donor	54	0.2298	0.372
Surgeon's Opinion	90	0.3669	0.621

The NOVEL and NOVEL Extension study enrolled previously unacceptable lungs that were offered multiple times to recipient sites and were not accepted, and were thus bound for disposal. For the donor lungs accepted for EVLP, the Organ Placement Organizations (OPOs) made an average of 23 placement attempts (median 9, range 1-199) before a study site accepted the organ for EVLP. This number of placement attempts is higher than the typical number for standard criteria lungs per Harhay et al., 2019, who claims that 70% of organs are placed by match sequence number 10. For most lungs, the OPO continued to attempt placement even after study enrollment due to the fact that the EVLP sites had asked for pump waivers, meaning that if the lung was evaluated not to be transplantable after EVLP, then they would not have to pay for the lung. In those cases where pump waivers were requested, the mean number of additional offers made was 30 (median 23, range 0-317), for a total of 53 refusals (median 32, range 1-383). Without the option of EVLP, the OPO would have stopped lung placement efforts at the last Match Attempt listed and these lungs would not have been used for transplant.

After EVLP, the following donor lung characteristics were noted.

Table 14 – Post-EVLP Donor Lung Evaluation

EVLP Run Data	NOVEL EVLP	
	Not Transplanted N = 106	Transplanted N = 110
Best PO2		
Best PaO2 (Mean)	98.4	102.0
Best PaO2 (Median)	92.5	91.0
Best Δ PO2 (Mean)	327.9	418.5
Best Δ PO2 (Median)	340.0	417.5
Key Parameters Influencing Decision to Transplant		
Median PAP (mmHg)	7.5	7.8
Median LAP (mmHg)	4.0	4.0
Median PVR (mmHg)	219.5	185.5
Median CStat (dynes)	85.0	103.0
Median PaO2 (Median)	84.0	82.0

The major reasons for not transplanting lungs after EVLP are summarized in Table 15.

Table 15 – Post-EVLP Donor Lung Evaluation

	EVLP Not Transplanted N=106*	
Reasons why EVLP-treated lungs were considered unacceptable for transplant		
Edema	83	(78%)
PaO2 ≤ 350 mmHg	77	(73%)
Surgeon's Clinical Decision	74	(70%)
Compliance	51	(48%)
Bronchial Finding	46	(43%)
PVR	38	(36%)
Airway Pressure	31	(29%)
Fluid Level in Pump	26	(25%)
Logistics	5	(5%)

*Only unique lungs are counted for this analysis (i.e., a bilateral set of lungs that was split between two (2) recipients is only counted once). One hundred eight (108) EVLP non-transplants were performed.

The cold ischemia time and total out of body time for the study are summarized in Tables 16 and 17, below. As expected, the cold ischemia time for EVLP donor lungs was higher than that observed in the control arm, and similarly, the total out-of-body time was higher in the EVLP arm, compared to the control.

Table 16 – Cold Ischemia Time

	EVLP N=110	Control N=111*
Quantiles		
100.0% Max	905	675
99.5%	905	675
97.5%	773	601
90.0%	688	459
75.0% Q3	595	390
50.0% Median	494	317
25.0% Q1	381	247
10.0%	287	179
2.5%	236	116
0.5%	195	111
0.0% Min	195	111
Summary Statistics		
Calculable	110	111
Not Calculable	0	5
Mean	494.4	320.4
Standard Deviation	146.0	108.8
Standard Error (Mean)	13.9	10.3
Upper 95% Mean	522.0	342.8
Lower 95% Mean	466.9	301.9
Interquartile range	214	143

*5 control subjects had incalculable total ischemic time.

Table 17 – Total Out of Body Time

	EVLP N=110	Control N=111*
Quantiles		
100.0% Max	1125	675
99.5%	1125	675
97.5%	1087	601
90.0%	928	459
75.0% Q3	830	390
50.0% Median	732	317
25.0% Q1	627	247
10.0%	519	179
2.5%	450	116
0.5%	375	111
0.0% Min	375	111
Summary Statistics		
Calculable	110	111
Not Calculable	0	5
Mean	735.4	322.4

	EVLP N=110	Control N=111*
Standard Deviation	157.0	108.8
Standard Error (Mean)	15.0	10.3
Upper 95% Mean	765.1	342.8
Lower 95% Mean	705.7	301.9
Interquartile range	203	143

*5 control subjects had incalculable total ischemic time.

The recipient characteristics for the study are summarized in Table 18.

Table 18 – Recipient Demographics

Donors	NOVEL EVLP N=110	NOVEL Control N=116	UNOS Control N=4898
Recipient Gender			
Female	41 37.3%	53 45.7%	1947 40.3%
Male	69 62.7%	63 54.3%	2924 59.7%
Recipient CMV			
Negative	51 46.4%	56 48.3%	2266 46.3%
Positive	59 53.6%	58 50.0%	2552 52.1%
Not Done	0 0.0%	2 1.7%	79 1.6%
Primary Diagnosis			
Emphysema/COPD/A1	48 43.6%	43 37.1%	1442 29.4%
Fibrosis	47 42.7%	42 36.2%	2836 57.9%
Cystic Fibrosis	7 6.4%	13 11.2%	505 10.3%
Primary Pulmonary HTN	0 0.0%	3 2.6%	115 2.4%
Other	8 7.3%	15 12.9%	Not available
Recipient Race			
Amerind/Alaska Native	0 0.0%	1 0.9%	Data not available from UNOS
Black/African American	6 5.5%	4 3.4%	
White	102 92.7%	111 95.7%	
Other	1 0.9%	0 0.0%	
Unknown	1 0.9%	0 0.0%	
Recipient Ethnicity			
Hispanic/Latino	4 3.6%	3 2.6%	Data not available from UNOS
Not Hispanic/Latino	104 94.5%	112 96.6%	
Unknown	2 1.8%	1 0.9%	
Transplanted Lung			
Bilateral	63 57.3%	81 69.8%	3491 71.3%
Single Left	25 22.7%	21 18.1%	772 15.8%
Single Right	22 20.0%	14 12.1%	635....13.0%
Single/Double			
Double	63 57.3%	81 69.8%	3491 71.3%
Single	47 42.7%	35 30.2%	1407 28.7%

D. Safety and Effectiveness Results

1. Safety and Effectiveness Results

Patient Survival

One of the components of the primary endpoint was one-year survival. The survival data (considering all cause mortality) are summarized in Table 19, below. As can be seen, survival for the EVLP Arm was worse than that observed in the Control Arm (86% vs. 94%, respectively), and the patient survival co-primary endpoint is not met according to the definitions pre-specified in the clinical protocol.

The Applicant categorized several deaths, seven (7) in the EVLP Arm and two (2) in the Control Arm, as "accidental" or adjudicated to have "Confounding Risk Factors," meaning that in the Applicant's assessment, they were deemed not related to the EVLP treatment, nor to the transplantation procedure. There was a provision in the clinical protocol for adjudicating deaths as "accidental (e.g., automobile accident)." When those "accidental" deaths are excluded from the analysis, the Applicant is able to meet non-inferiority (by the pre-specified delta of 12%), with a one-year survival rate of 93% for the EVLP Arm, compared to 96% for the Control Arm. This analysis introduces uncertainty, since it is difficult to assess bias in the adjudication. There were no "accidental deaths" related to accidents, such as automobile accidents. Table 19 provides the all-cause survival data; therefore, it includes the "accidental deaths." Similarly, Figure 3 provides the Kaplan-Meier curve for all-cause mortality. Table 20 lists the deaths occurring in the study, including the causes of death.

Table 19 – 1 Year Survival (All Cause Mortality) Rate Difference

One Year Survival (All Cause Mortality)	NOVEL EVLP N = 110		NOVEL Control N = 116		p-value (Fisher's)	UNOS Control N = 4063*	
Survived to 1 Year	95	(86%)	109	(94%)	0.0718	3556	(88%)
Expired Before 1 Year	15	(14%)	7	(6%)		507	(12%)
Case Not At 1 Year (not included in survival %)	0 of 110 cases		0 of 116 cases			835 of 4898 cases	
	0 living, 0 expired		0 living, 0 expired			793 living, 42 expired	

* Subjects transplanted less than 1 year from the cutoff date are not included in the analysis.

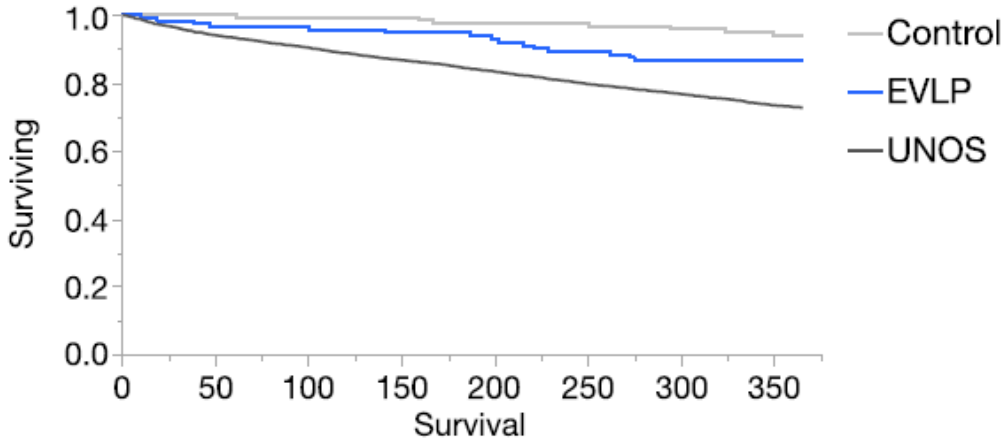
An independent three (3) member safety committee (comprised of two (2) lung transplant surgeons and one (1) lung transplant pulmonologist) performed a quarterly review of a listing of safety data for the EVLP and Control Arms to assess if the events that occurred outside of the expected events in this population. This included quarterly review and adjudication of all Major Lung Events (MLEs) and Deaths as per the study protocol safety charter. The committee reviewed causality, cause of death, MLE type, and

provided clinical justification for the deaths removed from the specific cause survival analysis. If an event was considered an Unanticipated Adverse Device Effect (UADE), the safety committee and the Independent Safety Monitor (ISM)adjudicated and assessed unreasonable risk.

In addition to the uncertainly over the "accidental" deaths, the Applicant has also expressed concerns regarding the NOVEL and NOVEL Extension's Control Group. They state that the Control Group was subject to selection bias, since some investigators in the study failed to enroll Control patients concurrently with their EVLP patients, as evidenced in the monitoring visits performed by the Applicant to their investigational sites. The Applicant states that the Control Group performance (e.g., 94% and 96% 12-month all cause mortality and specific mortality survival, respectively) is excessively high, and thus, the study's Control Group is not a fair comparator for the EVLP data.

To bring some perspective to the EVLP data, the Applicant has provided a comparison between the EVLP results and data from the United Network Organ Sharing (UNOS) Scientific Registry of Transplant Recipients (SRTR). The UNOS data provided are for transplants that took place during the time of the NOVEL and NOVEL Extension studies and were collected at the same investigational sites. They exclude the NOVEL patients (EVLP and Control), but are inclusive of all other transplants performed that fit the NOVEL study entry criteria. As can be seen, the patient survival data are comparable between the EVLP Arm and UNOS data (all-cause mortality survival rates of 86% for the EVLP Group and 88% for the UNOS Control Group). The Applicant states the comparison between the EVLP Group and the UNOS data is more indicative of real-world evidence.

Figure 3 – Kaplan-Meir Curve – NOVEL EVLP, NOVEL Control and UNOS – All Cause Mortality



Group	Number failed	Number Censored	p-value ChiSq
EVLP	15	95	Log-Rank: <0.001 Wilcoxon: <0.001 UNOS data is lower
NOVEL Control	7	109	
UNOS	1341	3557	
Combined	1363	3761	

Table 20 – Patient Deaths - First Twelve Months Post-Transplantation

Site	Subject	Study Arm	Diagnosis Requiring Tansplant	Date of Transplan	Date of Death	Primary Cause of Death
1	123	Control	Fibrosis	4/3/14	6/4/14	Antibody mediated rejection
3	301	EVLP	Fibrosis	10/5/11	10/15/11	Reperfusion injury due to cytokines
3	302	Control	Fibrosis associated with short telomere	1/20/12	9/26/12	Renal failure
4	409	EVLP	Fibrosis	4/22/12	11/10/12	Respiratory failure
4	412	EVLP	Fibrosis	10/4/12	2/22/13	Acute rejection
4	427	Control	Emphysema, COPD, Alpha 1 Antitrypsin Deficiency	7/15/17	12/29/17	Acute on chronic hypercarbic respiratory failure
5	504	Control	Fibrosis	3/3/12	8/9/12	Airway stenonis and respiratory failure
5	513	EVLP	Fibrosis	7/18/12	2/1/13	Complications from aortic injury

Site	Subject	Study Arm	Diagnosis Requiring Tansplant	Date of Transplan	Date of Death	Primary Cause of Death
5	522	EVLP	Emphysema/COPD/ Alpha 1 Antitrypsin Deficiency	9/12/12	6/11/13	BOS, B-cell lymphoma/leukemia which caused a discontinuation of immunosuppression
5	572	EVLP	Emphysema/COPD/ Alpha 1 Antitrypsin Deficiency	5/21/17	12/22/17	Bacterial septicemia
6	609	EVLP	Fibrosis	3/2/13	10/17/13	Massive hemoptysis secondary to a bronchovascular fistula that occurred following stent placement due to bronchial stenosis
6	620	EVLP	Emphysema/COPD/ Alpha 1 Antitrypsin Deficiency	6/17/13	12/21/13	Renal failure
6	625	EVLP	Emphysema/COPD/ Alpha 1 Antitrypsin Deficiency	11/3/13	8/5/14	Lung cancer (RLL squamous cell carcinoma)
6	630	EVLP	Emphysema/COPD/ Alpha 1 Antitrypsin Deficiency	6/16/15	7/5/15	Liver failure
6	640	EVLP	Emphysema/COPD/ Alpha 1 Antitrypsin Deficiency	12/20/16	9/8/17	Lymphoma
7	703	EVLP	Emphysema/COPD/ Alpha 1 Antitrypsin Deficiency	7/16/13	2/22/14	Graft vs. Host Disease
8	809	Control	Emphysema/COPD/ Alpha 1 Antitrypsin Deficiency	3/6/15	12/25/15	Septic shock caused by aspiration pneumonia
9	905	EVLP	Fibrosis	10/12/16	11/28/16	Sepsis due to colon perforation with diverticulitis
11	1105	Control	Scleroderma	5/13/15	4/26/16	Intracranial hemorrhage
11	1111	EVLP	Emphysema/COPD/ Alpha 1 Antitrypsin Deficiency	3/9/17	7/17/17	Septic shock
16	1603	EVLP	Fibrosis	3/22/17	4/30/17	Cardiopulmonary arrest

Site	Subject	Study Arm	Diagnosis Requiring Tansplant	Date of Transplan	Date of Death	Primary Cause of Death
17	1705	Control	Fibrosis	9/25/16	8/15/17	Respiratory failure, sepsis

The deaths adjudicated by the Applicant and their independent Safety Committee as being "accidental" or unrelated to the device are:

- Unrelated control deaths: 302, 1105
- Unrelated EVLP deaths: 513, 620, 625, 640, 703, 905, 1111

As discussed earlier, when looking at all-cause mortality, the NOVEL study does not meet its pre-specified primary endpoint, which includes 12-month survival. Instead of falling within the pre-specified 12% non-inferiority margin, the observed value for survival for the EVLP Arm is 15% different (worse) than the Control Group (as indicated by the upper bound of the two-sided 95% confidence interval). FDA concludes that the all-cause mortality data should be used when describing the survival co-primary endpoint, since that was the analysis pre-specified in the clinical protocol. As such, EVLP subjects fared worse than the Control Group, although the concerns raised by the Applicant about the Control Group should be considered. The FDA also believes the comparison of the NOVEL EVLP data to data collected from UNOS is valuable and can provide an indication of where EVLP-treated lungs might fit in the lung transplant field.

PGD Grade

The second component of the primary endpoint was the incidence of PGD Grade 3 at 72 hours post-transplantation. Table 21 shows the PGD data for 24, 48 and 72 hours post-transplantation before adjudication. Considering these unadjudicated data, the PGD Grade 3 at 72 hours post-transplantation were 14% for the EVLP Group vs. 7% for the Control Group. This comparison does not meet the success criteria pre-specified in the clinical protocol.

The PGD data were adjudicated by the Applicant's Clinical Events Committee. During adjudication, there were nine (9) patients (all in the EVLP arm) who were deemed to have received prophylactic Extracorporeal Membrane Oxygenation (ECMO). These were patients who were placed on ECMO prior to the transplantation surgery and were then kept on ECMO post-transplantation until they recovered sufficient function. According to the protocol, any patient on ECMO when assessed for PGD would be automatically graded Grade 3, per the International Society for Heart and Lung Transplantation (ISHLT) guidelines; however, according to the study's Statistical Analysis Plan, these "prophylactic" ECMO patients would be excluded from the primary analyses. As shown below, the incidence of PGD Grade 3 at 72 hours post-transplantation was higher in the EVLP Arm, compared to Control, and when all ECMO patients are included in the

analyses, pre-specified 12% non-inferiority is not met. When the prophylactic ECMO patients are excluded, however, the PGD Grade 3 rates are more comparable. Retrospectively, it is difficult to determine whether patients on ECMO therapy are being truly treated prophylactically, or if they are being given ECMO therapeutically. As such, the Summary of Safety and Effectiveness Data (SSED) and labeling include all Grade 3 subjects, even if Grade 3 is due to ECMO. After independent adjudication, but still including all ECMO subjects, the PGD Grade 3 rates were 16% and 9% in the control and EVLP Groups, respectively.

The PGD Grade 3 data at 72-hours post-transplantation does have a favorable comparison to the UNOS control data provided by the sponsor (31.3% Grade 3 at 72 hours post-transplantation, N=1200), although it should be noted that PGD grade data are not always available in the SRTR database, and the SRTR registry is not a reliable comparator for PGD. Looking at other comparators, the Applicant has cited the Lung Transplant Outcomes Group (LTOG), which was a U.S. National Institutes of Health (NIH) sponsored, multicenter, prospective cohort study designed to evaluate risk factors for, and rates of, PGD. This study included 10 centers and its primary outcome was PGD at 48 or 72 hours post-transplantation. According to the LTOG data, the rate of PGD Grade 3 at 72 hours post-transplantation was 16.8% (Diamond et al., 2013), which compares favorably with the NOVEL and NOVEL Extension EVLP 72-hour PGD data, which was 16%. Additionally, per Christie et al., 2005, the national incidence of 72-hour Grade 3 PGD is between 10% and 30%.

In order to monitor safety in real-time and continually assess the safety of the device, the Safety Committee was un-blinded to Treatment Arms and could not be used to adjudicate PGD at 72 hours, as this could bias the adjudication. Accordingly, all of the 72-hour PGD scores were adjudicated by 2 blinded independent transplant pulmonologists per the study protocol. The adjudicators' responsibility was to perform PGD adjudication to determine PGD score based on the 72 hour raw, blinded, de-identified chest x-ray images and a clinical database extract of Arterial Blood Gases (ABGs) using the ISHLT Determination. If there was non-consensus between the Investigator and Primary Adjudicator, all reports and images were reviewed and assessed by a secondary adjudicator. The majority PGD score determined the final score. When one adjudicator provided a score of 3, which was not in consensus with the other adjudicator, a second adjudicator review took place. If there was a non-consensus decision between the investigator, primary adjudicator, and secondary adjudicator, a second adjudicator review took place and a consensus was made between the Primary and Secondary adjudicator.

Table 21 – Primary Graft Dysfunction – Unadjudicated and Including Prophylactic ECMO – 24, 48 and 72 hours Post-Transplantation

@ 24 Hours	EVLP N = 110		Control N = 116		p-value (χ2)
Grade 0	24	(22%)	29	(25%)	0.0294
Grade 1	34	(31%)	46	(40%)	
Grade 2	24	(22%)	29	(25%)	
Grade 3	28	(25%)	12	(10%)	
@ 48 Hours	**EVLP N = 110**		**Control N = 116**		**p-value (χ2)**
Grade 0	30	(27%)	29	(25%)	0.4847
Grade 1	47	(43%)	55	(47%)	
Grade 2	16	(15%)	21	(18%)	
Grade 3	17	(15%)	11	(9%)	

@ 72 Hours

All Subjects	EVLP N = 110		Control N = 116		p-value (χ2)
Grade 0	37	(34%)	37	(32%)	0.3387
Grade 1	42	(38%)	53	(46%)	
Grade 2	16	(15%)	18	(16%)	
Grade 3	15	(14%)	8	(7%)	

Other Safety and Effectiveness Data

Additional safety data are summarized in the tables below, including Intensive Care Unit length of stay, hospital length of stay, duration of mechanical ventilation, pulmonary function data, delayed extubations, re-intubations and tracheostomies, and ECMO use. These parameters show comparable performance between the EVLP and Control Groups.

Table 22 – Intensive Care Unit (ICU) Length of Stay (LOS, days)

ICU Length of Stay	NOVEL EVLP N = 110	NOVEL Control N = 116
Mean LOS	9.9	9.8
Standard Deviation	14.4	18.7
25th Percentile	3	2
Median LOS	5	4.5
75th Percentile	9	9
Interquartile Range	6	7
Expired Prior to ICU Discharge	4	0

Table 23 – Hospital Length of Stay (LOS, days)

Hospital Length of Stay	NOVEL EVLP N = 110	NOVEL Control N = 116
Mean LOS	23.9	28.5
Standard Deviation	24.4	41.7
25th Percentile	11	10.25
Median LOS	16	14.5
75th Percentile	24.75	24.25
Interquartile Range	13.75	14
Expired Prior to Hospital Discharge	5	0

Table 24 – Duration of Mechanical Ventilation (days)

Intubation	NOVEL EVLP N = 110	NOVEL Control N = 116
Mean LOS	7.0	5.7
Standard Deviation	24.7	21.8
25th Percentile	1	1
Median LOS	1	1
75th Percentile	3.75	2
Interquartile Range	2.75	1
Expired Prior to Extubation	2	0

Table 25 – Pulmonary Function Test – FEV1% (Predicted) – at 3, 6, 9, 12 Months

	3 Months		6 Months		9 Months		12 Months	
FEV1	EVLP N = 110	Control N = 116	EVLP N = 110	Control N = 116	EVLP N = 110	Control N = 116	EVLP N = 110	Control N = 116
Mean	69	73	71	74	72	74	72	76
Median	69	72	70	71	72	72	72	75
Range	(19-111)	(22-125)	(22-123.8)	(26-136)	(28-120)	(26-150)	(23-115)	(21-144)
*Not Done**	11	9	14	9	21	9	20	11

* A +/- 30 day window was allowed on all PFT evaluations. A PFT evaluation may not have been performed if the subject expired close to the 1/2/3 year timepoint, or if the subject was trached or hospitalized at the scheduled time of evaluation.

Table 26 – Delayed Extubations, Re-Intubations and Tracheostomies

	EVLP N = 110		Control N = 116		p-value Fisher's
Delayed Extubation					
Extubated Within 96 Hours of TX	91	(83%)	101	(87%)	0.4570
Not Extubated Within 96 Hours of TX	19	(17%)	15	(13%)	
Re-Intubations					
Not Re-Intubated After Initial Extubation	88	(80%)	91	(78%)	0.8700
Re-Intubated Within 1 Year of TX	22	(20%)	25	(22%)	
Tracheostomies (Due to Respiratory Failure)					
Not Trached Within 1 Year of TX	94	(85%)	99	(85%)	1.0000
Trached Within 1 Year of TX	16	(15%)	17	(15%)	

Table 27 – ECMO Use and PFT Data

	Count		Average ECMO Days	FEV1 @3M	FEV1 @6M	FEV1 @9M	FEV1 @12M
EVLP							
All Subjects	110	(NA)	NA	69.0	70.6	72.2	72.0
No ECMO At Any Point	87	(79%)	NA	69.0	69.9	70.9	70.7
Intraoperative ECMO	23	(21%)	8.5	69.2	73.5	77.8	77.8
Prophylactic Use *(% of intraop)*	7	(30%)	2.0	71.0	69.9	75.9	75.2
Non-Prophylactic *(% of intraop)*	16	(70%)	11.4	68.3	76.0	79.1	79.4
Postoperative ECMO	1	(1%)	4.0	65.0	72.0	72.0	72.0
Control							
All Subjects	116	(NA)	NA	72.9	74.2	74.0	75.7
No ECMO At Any Point	101	(87%)	NA	73.6	75.8	76.0	78.0
Intraoperative ECMO	15	(13%)	0.3	67.3	63.9	61.8	61.9
Prophylactic Use *(% of intraop)*	5	(33%)	0.4	69.3	69.2	68.8	68.2
Non-Prophylactic *(% of intraop)*	10	(67%)	0.2	66.3	61.0	58.3	58.8
Postoperative ECMO	7	(6%)	14.3	41.0	44.4	43.0	39.7

Adverse events that occurred in the PMA clinical study:

The Applicant has provided information on adverse events, including the rates of MLEs, such as acute rejection, bronchial complications, respiratory failure, infections and re-transplantations, as well as non-MLEs and hospitalizations. These appear clinically comparable. Tables 28 and 29 provide the MLE data. The serious and non-serious MLEs listed separately in Table 29 are a subset of the overall MLE data provided in Table 28.

Table 28 – Major Lung Events (MLEs) Serious and Non-Serious Combined.

Combined MLEs by Type	EVLP 182 Events		Control 176 Events	
Acute Rejection	34	(19%)	32	(18%)
Bronchial Complication	19	(10%)	12	(7%)
Respiratory Failure	45	(25%)	53	(30%)
Major Pulmonary Infection	84	(46%)	79	(45%)
Re-Transplant	0	(0%)	0	(0%)
Combined MLE Rate	**EVLP (N = 110)**		**Control (N = 116)**	
Combined MLE Rate per Subject				
Average # of MLEs	1.65		1.52	
Range	(0 - 7)		(0 - 6)	

Table 29 – Breakdown of Serious and Non-Serious Major Lung Events

Serious MLEs by Type	EVLP 130 Events		Control 138 Events	
Acute Rejection	24	(13%)	17	(10%)
Bronchial Complication	10	(5%)	10	(6%)
Respiratory Failure	44	(24%)	52	(30%)
Major Pulmonary Infection	52	(29%)	59	(34%)
Re-Transplant	0	(0%)	0	(0%)
Serious MLE Rate	**EVLP (N = 110)**		**Control (N = 116)**	
Serious MLE Rate per Subject				
Average # of MLEs	1.18		1.19	
Range	(0 - 6)		(0 - 6)	

Non-Serious MLE Rate	EVLP (N = 110)	Control (N = 116)
Non-Serious MLE Rate per Subject		
Average # of MLEs	0.47	0.33
Range	(0 - 5)	(0 - 5)

Table 30 - Non-Major Lung Event Hospitalizations

	EVLP		Control	
Non-MLE Hospitalizations				
Total Hospitalizations	150		208	
Pulmonary (non-MLE)	47	(31%)	57	(27%)
Gastrointestinal	39	(26%)	50	(24%)
Renal	11	(7%)	18	(9%)
Cardiovascular / Vascular	9	(6%)	24	(12%)
Neurological	8	(5%)	10	(5%)
Infection	7	(5%)	14	(7%)
Post-Transplant Complication	6	(4%)	8	(4%)
Hematology	4	(3%)	5	(2%)
Integumentary	2	(1%)	1	(0%)
Musculoskeletal	2	(1%)	4	(2%)
ENT	1	(1%)	1	(0%)
Endocrine	0	(0%)	2	(1%)
Other Indication*	14	(9%)	13	(6%)
Significant Non-Pulmonary Infections from Transplant to 30 Days				
Total SNPIs	8		3	

* "Other" Indications for EVLP Subjects: Prophylactic treatment for meningitis & flu, nausea & vomiting secondary to metoprolol, false liver function test rise, hyperkalemia (x3), hypersensitivity reaction, systemic inflammatory response syndrome, human herpes virus 6/graft vs. host disease, facial swelling, requires pressure support at night (x3)
"Other" Indications for Control Subjects: Deconditioning (x2), allergic reaction & volume overload, hyperkalemia, systemic inflammatory response syndrome, afib/vertigo/pain, afib/syncope, multi-system failure, shock, failure to thrive (x2), malnutrition and dehydration, lethargy

Additionally, the following more detailed safety data, including the incidence of pneumonia and other infections, are summarized below.

Table 31 – Pneumonia/Major Pulmonary Infections

	EVLP N = 110		Control N = 116		p-value χ^2
During Initial Hospitalization					
Subjects with no MPIs	94	(85%)	102	(88%)	0.6546
Subjects with confirmed pneumonia	6	(5%)	4	(3%)	
*Subjects with microbial infection**	9	(8%)	10	(9%)	
Subjects with non-pneumonia infection	1	(1%)	0	(0%)	
After Initial Hospitalization					
Subjects with no MPIs	64	(58%)	69	(59%)	0.8285
Subjects with confirmed pneumonia	22	(20%)	25	(22%)	
*Subjects with microbial infection**	20	(18%)	20	(17%)	
Subjects with non-pneumonia infection	4	(4%)	2	(2%)	

* Microbes identified via bronchoscopy or sputum, treated but not confirmed as pneumonia..

The rate of pneumonia and major pulmonary infections was comparable between the 2 arms of the study.

Quality of Life:

The following quality of life data were presented for the 12-month post-transplantation point. As can be seen, the EVLP and Control Groups were comparable.

Table 32 – Quality of Life Data

	1 Year			
	EVLP Reached 1 Year N = 95 Expired <1 Year 15 Not Yet At 1Y 0		Control Reached 1 Year N = 109 Expired <1 Year 7 Not Yet At 1Y 0	
Functional Status				
No Limitations	83	(87%)	91	(83%)
ADLs With Some Assistance	5	(5%)	13	(12%)
ADLs With Total Assistance	0	(0%)	1	(1%)
Subject Hospitalized	2	(2%)	0	(0%)
Unknown	4	(4%)	4	(4%)
Data Pending	1	(1%)	0	(0%)
Physical Capacity				
No Limitations	83	(87%)	93	(85%)
Limited Mobility	5	(5%)	10	(9%)
Wheelchair or More Limited	0	(0%)	0	(0%)
Subject Hospitalized	2	(2%)	0	(0%)
Unknown	4	(4%)	5	(5%)
Data Pending	1	(1%)	1	(1%)
Employment Status				
Working Full Time	4	(4%)	5	(5%)
Working Part Time	2	(2%)	1	(1%)
Working, Amount Unknown	6	(6%)	1	(1%)
Not Working	51	(54%)	70	(64%)
Unknown	37	(39%)	33	(30%)
Data Pending	1	(1%)	0	(0%)
Reason for Not Working	EVLP N = 51		Control N = 70	
Due to Disability	7	(14%)	10	(14%)
Demands of Treatment	3	(6%)	3	(4%)
Personal Choice / Retirement	28	(55%)	35	(50%)
Unknown	13	(25%)	20	(29%)

Protocol Deviations:

The Applicant has provided a list of the protocol deviations reported for the study. A total of 65 protocol deviations are listed, occurring at the majority of investigational sites. Many of the deviations occurred in the early days of the

study. Common protocol deviations were:

- Use of incorrect version of Informed Consent form;
- Donor lungs not meeting the study entry criteria or transplantability criteria (i.e., criteria to undergo EVLP and/or post-EVLP transplantabiltiy criteria);
- Missed data collections (e.g., lung x-rays);
- EVLP run times too long or short (too long refers to deviations that occurred before the clinical protocol was revised to allow for EVLP for up to 6 hours);
- Continued EVLP despite malfunction of venous gas mixture tank (lungs treated in this case underwent their post-EVLP assessment and would have to meet the specified transplantability criteria in order to proceed to transplant).

These protocol deviations were not considered clinically significant or concerning.

2. Subgroup Analyses

The following donor lung and recipient characteristics were evaluated for potential association with outcomes: donation after cardiac death (DCD) donor lungs, recipient gender, recipient diagnosis and type of transplant (i.e., single vs. double).

Table 33 – Overall Survival – Brain Dead vs. Donation after Cardiac Death Donor Lungs (BD/DCD)

30 Day Mortality	NOVEL EVLP		NOVEL Control		UNOS Control*	
	BD N = 82	DCD N = 28	BD N = 116	DCD NA	BD N = 4729	DCD N = 106
Survived to 30 Days	80	28	116	NA	4596	105
Expired Before 30 Days	2	0	0	NA	133	1
Overall Survival	98%	100%	100%	NA	97%	99%
1 Year Mortality	**NOVEL EVLP**		**NOVEL Control**		**UNOS Control***	
	BD N = 82	DCD N = 28	BD N = 116	DCD NA	BD N = 3974	DCD N = 89
Survived to 1 Year	70	25	109	NA	3475	81
Expired Before 1 Year	12	3	7	NA	499	8
Overall Survival	85%	89%	94%	NA	87%	91%

** Subjects transplanted less than 30/365 days of the date the data set was obtained were not counted in this analysis. Of 4898 total UNOS controls transplanted, 4835 were transplanted greater than 30 days prior to the cutoff date, and 4063 were transplanted greater than 365 days prior to the cutoff date.*

Table 34 – Overall Survival by Gender

30 Day Mortality	NOVEL EVLP		NOVEL Control		UNOS Control*	
	Male N = 69	Female N = 41	Male N = 63	Female N = 53	Male N = 2886	Female N = 1949
Survived to 30 Days	67	41	63	53	2797	1904
Expired Before 30 Days	2	0	0	0	89	45
Overall Survival	97%	100%	100%	100%	97%	98%
1 Year Mortality	**NOVEL EVLP**		**NOVEL Control**		**UNOS Control***	
	Male N = 69	Female N = 41	Male N = 63	Female N = 53	Male N = 2452	Female N = 1611
Survived to 1 Year	58	37	60	49	2108	1448
Expired Before 1 Year	11	4	3	4	344	163
Overall Survival	84%	90%	95%	92%	86%	90%

** Subjects transplanted less than 30/365 days of the date the data set was obtained were not counted in this analysis. Of 4898 total UNOS controls transplanted, 4835 were transplanted greater than 30 days prior to the cutoff date, and 4063 were transplanted greater than 365 days prior to the cutoff date.*

Table 35 – Overall Survival by Diagnosis – Fibrosis/Pulmonary Hypertension (PPH) + vs. Fibrosis/PPH -

30 Day Mortality	NOVEL EVLP		NOVEL Control		UNOS Control*	
	F/PPH + N = 47	F/PPH - N = 63	F/PPH + N = 45	F/PPH - N = 71	F/PPH + N = 2914	F/PPH - N = 1921
Survived to 30 Days	46	62	45	71	2828	1873
Expired Before 30 Days	1	1	0	0	86	48
Overall Survival	98%	98%	100%	100%	97%	98%
1 Year Mortality	**NOVEL EVLP**		**NOVEL Control**		**UNOS Control***	
	F/PPH + N = 47	F/PPH - N = 63	F/PPH + N = 45	F/PPH - N = 71	F/PPH + N = 2430	F/PPH - N = 1633
Survived to 1 Year	40	55	42	67	2092	1464
Expired Before 1 Year	7	8	3	4	338	169
Overall Survival	85%	87%	93%	94%	86%	90%

** Subjects transplanted less than 30/365 days of the date the data set was obtained were not counted in this analysis. Of 4898 total UNOS controls transplanted, 4835 were transplanted greater than 30 days prior to the cutoff date, and 4063 were transplanted greater than 365 days prior to the cutoff date.*

Table 36 – Overall Survival by Single and Double Lung Transplantation

30 Day Mortality	NOVEL EVLP		NOVEL Control		UNOS Control*	
	Single N = 47	Double N = 63	Single N = 35	Double N = 81	Single N = 1392	Double N = 3443
Survived to 30 Days	46	62	35	81	1354	3347
Expired Before 30 Days	1	1	0	0	38	96
Overall Survival	98%	98%	100%	100%	97%	97%
1 Year Mortality	**NOVEL EVLP**		**NOVEL Control**		**UNOS Control***	
	Single N = 47	Double N = 63	Single N = 35	Double N = 81	Single N = 1206	Double N = 2857
Survived to 1 Year	40	55	33	76	1039	2517
Expired Before 1 Year	7	8	2	5	167	340
Overall Survival	85%	87%	94%	94%	86%	88%

** Subjects transplanted less than 30/365 days of the date the data set was obtained were not counted in this analysis. Of 4898 total UNOS controls transplanted, 4835 were transplanted greater than 30 days prior to the cutoff date, and 4063 were transplanted greater than 365 days prior to the cutoff date.*

These data follow the general trends observed in the overall survival data and no inferences can be made regarding the use of the XPS™ System in these patient subgroups, due to the small sample size.

3. Long-term Safety and Effectiveness Results

Although the NOVEL study and its extension were designed to follow subjects for up to 12 months post-transplantation, and the primary endpoints are tied to that time point, the Applicant has collected longer term data through the PAS from H120003. This PAS followed the NOVEL and NOVEL Extension patients to 3 years post-transplantation. Data collection is ongoing and not all patients have completed the PAS, but 83 of the 110 EVLP subjects (75%) and 87 of the 116 Control subjects (75%) have reached the 2-year post-transplantation point, while 70 (64%) of EVLP subjects and 73 (63%) of the Control subjects are out to 3 years post-transplantation (see Table 38). The long-term patient status data showing all cause mortality are summarized in Table 37, below.

Table 37 – Subject Status (Cumulative)

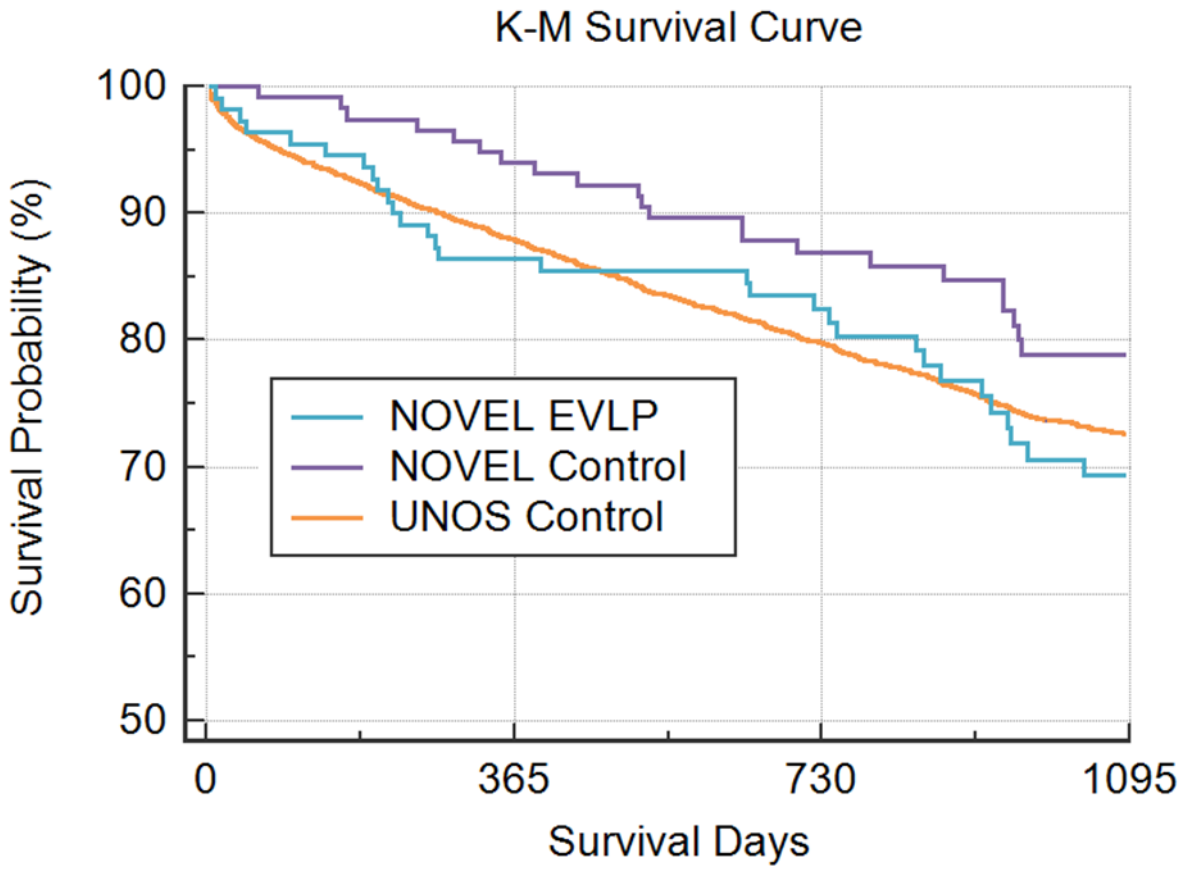
	30 Day				1 Year			
	EVLP N = 110		Control N = 116		EVLP N = 110		Control N = 116	
Active On Study at Time Point	108	(98%)	116	(100%)	95	(86%)	109	(94%)
Subjects Expired at Time Point	2	(2%)	0	(0%)	15	(14%)	7	(6%)
Subjects Retransplanted	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Subjects Lost to Follow-Up	0	(0%)	0	(0%)	0	(0%)	0	(0%)
PAS 2 and 3 year Timepoint	**2 Year**				**3 Year**			
	EVLP N = 110		Control N = 116		EVLP N = 110		Control N = 116	
Active On Study at Time Point	90	(82%)	101	(87%)	79	(72%)	94	(81%)
Subjects Expired at Time Point	19	(17%)	15	(13%)	30	(27%)	22	(19%)
Subjects Retransplanted	1	(1%)	0	(0%)	1	(1%)	0	(0%)
Subjects Lost to Follow-Up	0	(0%)	0	(0%)	0	(0%)	0	(0%)

The 2- and 3-year overall survival data (all cause mortality) are given in Table 38 and the Kaplan-Meier curve generated for these data is presented in Figure 4.

Table 38 – Overall Survival (EVLP vs. Control) Including UNOS data– Out to Three Years Post-Transplantation – All Cause Mortality

One Year Survival (All Cause Mortality)	**NOVEL EVLP N = 110**		**NOVEL Control N = 116**		**p-value** (Fisher's)	**UNOS Control N = 4063**	
Survived to 1 Year	95	(86%)	109	(94%)	0.0718	3556	(88%)
Expired Before 1 Year	15	(14%)	7	(6%)		507	(12%)
Case Not At 1 Year (not included in survival %)	0 of 110 cases 0 living, 0 expired		0 of 116 cases 0 living, 0 expired			835 of 4898 cases 793 living, 42 expired	
Two Year Survival (All Cause Mortality)	**NOVEL EVLP N = 83**		**NOVEL Control N = 87**		**p-value** (Fisher's)	**UNOS Control N = 3309**	
Survived to 2 Years	69	(83%)	76	(87%)	0.5180	2602	(79%)
Expired Before 2 Years	14	(17%)	11	(13%)		707	(21%)
Case Not At 2 Years (not included in survival %)	27 of 110 cases 22 living, 5 expired		29 of 116 cases 25 living, 4 expired			1589 of 4898 cases 1444 living, 145 exp.	
Three Year Survival (All Cause Mortality)	**NOVEL EVLP N = 70**		**NOVEL Control N = 73**		**p-value** (Fisher's)	**UNOS Control N = 2565**	
Survived to 3 Years	49	(70%)	56	(77%)	0.4494	1810	(71%)
Expired Before 3 Years	21	(30%)	17	(23%)		755	(29%)
Case Not At 3 Years (not included in survival %)	40 of 110 cases 31 living, 9 expired		43 of 116 cases 38 living, 5 expired			2333 of 4898 cases 2027 living, 306 exp.	

Figure 4 – Kaplan-Meier Survival Curve (All-Cause Mortality)* from Transplant to 3 Years



*- The UNOS control comparisons are post-hoc and were not pre-specified in the Statistical Analysis Plan.

An important aspect of long-term lung function post-transplantation is the evaluation of the incidence of BOS. The Applicant has provided BOS data for 1, 2, and 3 years post-transplantation. These data were collected as part of the H120003 PAS. The data are summarized in Table 39, below. Similarly, lung function data in terms of FEV1% are given in Table 40.

Table 39 – BOS Observed at 1, 2, and 3 Years

One Year				
	EVLP		Control	
	Reached 1Y Not at 1Y	110 0	Reached 1Y Not at 1Y	116 0
No BOS Observed	65	(87%)	76	(85%)
BOS Observed	10	(13%)	13	(15%)
Not Evaluable				
Subject Expired	15	35	7	27
*Not Done/Outstanding**	20		20	
Two Years				
	EVLP		Control	
	Reached 2Y Not at 2Y	95 15	Reached 2Y Not at 2Y	103 13
No BOS Observed	52	(84%)	68	(88%)
BOS Observed	10	(16%)	9	(12%)
Not Evaluable				
Subject Expired	12	33	6	26
*Not Done/Outstanding**	21		20	
Three Years				
	EVLP		Control	
	Reached 3Y Not at 3Y	74 36	Reached 3Y Not at 3Y	78 38
No BOS Observed	37	(84%)	50	(93%)
BOS Observed	7	(16%)	4	(7%)
Not Evaluable				
Subject Expired	10	30	7	24
*Not Done/Outstanding**	20		20	

* A +/- 30 day window was allowed on all BOS evaluations. A BOS evaluation may not have been performed if the subject expired close to the 1/2/3 year timepoint, or if the subject was trached or hospitalized at the scheduled time of evaluation.

Table 40 – Pulmonary Function Test FEV1% at 1, 2, and 3 Years

FEV1	1 Year		2 Years		3 Years	
	EVLP N = 95*	Control* N = 109*	EVLP* N = 69*	Control* N = 76*	EVLP* N = 49*	Control* N = 56*
Mean	72	76	67	73	70	74
Median	72	75	70	73	70	73
Range	(23-115)	(21-144)	(3.04-127)	(2-146)	(10-133)	(20-155)
*FEV1 Not Obtained***	5	4	6	5	12	10

* Only living subjects who had reached the 2/3 year timepoint were not included in the analysis.
** A +/- 30 day window was allowed on PFT evaluations. A PFT evaluation may not have been performed if the subject expired close to the 1/2/3 year timepoint, or if the subject was trached or hospitalized at the scheduled time of evaluation.

4. Pediatric Extrapolation

In this premarket application, existing clinical data were 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 17 investigators of which none were full-time or part-time employees of the sponsor and one had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none;
- Significant payment of other sorts: 1 investigator;
- Proprietary interest in the product tested held by the investigator: none;
- Significant equity interest held by investigator in sponsor of covered study: none.

The Applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. 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 Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety and Effectiveness Conclusions

The data from the NOVEL and NOVEL Extension have raised uncertainty regarding the safety and effectiveness of the proposed device. Although the peri-operative and 30-day performance of the device (e.g., PGD, survival, lung function, adverse events) are consistent with the results provided in H120003, the 12-month survival data and PGD Grade 3 at 72 hours co-primary endpoints did not meet non-inferiority compared to the Control Arm, with the pre-specified 12% non-inferiority margin. The 2- and 3- year survival data for the EVLP Arm also appear inferior (i.e., worse) compared to the Control. However, these findings should be assessed within the totality of the data, the fact that there are uncertainties with the enrollment of subjects in the Control Arm, which may have led to higher than expected survival, and the fact that these are previously unacceptable lungs that would have been discarded and yet were used in transplant procedures that yielded clinically acceptable outcomes.

Outcomes

For the co-primary endpoint of 1-year survival, a comparison of All-Cause Mortality was made between the EVLP and NOVEL Control Groups. The pre-determined 12% non-inferiority margin was missed for the endpoint of All-Cause Mortality at 1 year when comparing the NOVEL Control arm (94%), to the EVLP arm (86%).

The NOVEL and NOVEL Extension trial meets the primary end points using the post hoc analysis of Lifetime Survival Analysis (Specific Cause Mortality), defined as All-Cause Mortality with adjudicated Confounding Risk Factors Mortality excluded from the analyses. The Safety Committee was responsible for the adjudication of all Major Lung Events, Deaths and Lifetime Survival Analysis for the duration of the study. The Lifetime Survival Analysis (Specific Cause Mortality) is used to attempt to isolate a more specific clinical assessment of the risks of EVLP when employed in a high-risk patient population undergoing a high-risk surgical procedure. For the Lifetime Survival Analysis (Specific Cause Mortality), 9 patient deaths were excluded (7 in the EVLP group and 2 in the control group). This resulted in 12-month survival rates of 96% and 93% in the Control and EVLP Groups, respectively. This analysis introduces uncertainty, since it is difficult to assess bias in the adjudication.

The long-term survival of the EVLP and NOVEL Control arms is not clinically significantly different, as demonstrated by the 2-year (EVLP 83%, NOVEL Control 87%) and 3-year (EVLP 70%, NOVEL Control 77%) survival data.

Post-hoc analyses were performed comparing the EVLP data to those from the UNOS SRTR registry. The UNOS Control Group consisted of patients transplanted at the same centers as used for the NOVEL/NOVEL Extension study at the same period of time. The UNOS Control Group excluded EVLP patients, patients enrolled in the NOVEL/NOVEL Extension study, and it filtered subjects according to the NOVEL/NOVEL Extension study criteria. According to this analysis, the all-cause mortality 12-month survival rate in the EVLP Group of the study was similar to that in the UNOS Control Group (86% for EVLP vs. 88% for UNOS Control Group). The long-term survival of the EVLP Group is also similar to the UNOS Control Group at the 2- and 3-year post-transplantation point (83% and 70% for the EVLP Group for 2- and 3-years, respectively, vs. 79% and 71% for the UNOS Control Group for 2- and 3-years, respectively).

For the 72-hour PGD Grade 3 co-primary endpoint, a comparison between the EVLP and Control Groups in the NOVEL/NOVEL Extension trials resulted in missing the pre-determined 12% non-inferiority margin (14% incidence of Grade 3 PGD in the EVLP Group vs. 7% in the Control Group, unadjudicated data including all subjects on ECMO). When evaluating these data after adjudication (by independent, blinded pulmonologists), the rates were 16% for the EVLP Group and 9% for the Control Group.

A further post-hoc comparison of PGD Grade 3 at 72 hours was made between the EVLP Group and the LTOG dataset. The LTOG dataset is comprised of data collected between 2002 and 2010. Taking into consideration the inherent limitations of a retrospective, post-hoc analysis, the EVLP Group (16%) demonstrated a similar PGD Grade 3 rate at 72 hours post-transplantation to the published LTOG rate (16.8%) from Diamond et al., 2013.

The donor baseline characteristics showed that most of the donors (90%) were young (≤ 54 years old) with median age of 34-36, and most of the donor characteristics were similar across the EVLP and Control Groups, except for the inclusion of DCD donors in the EVLP Group (31% of all EVLP lungs) versus none in the Control, and the acceptance of lower PaO2 donor lungs for EVLP vs.the donor lungs in the Control Group (EVLP transplant median PaO2 of 344.5 versus Control Group PaO2 of 418.5). Sixty eight DCD donor lungs were enrolled in the EVLP group and underwent treatment, after which 28 (41%) were transplanted and 40 (59%) were discarded.

The majority of recipients were allocated in the low priority Lung Allocation Score (LAS) groups.

There were no marked differences in secondary endpoints, such as ICU length of stay, hospital length of stay, and duration of mechanical ventilation between the EVLP and Control Groups.

There were no significant differences in pulmonary infections, rejections, bronchial complications, and/or respiratory failures between the EVLP and Control Groups. Due to patient deaths, intubations/tracheostomies, and hospitalizations, there was a

10% to 18% missing data rate for FEV1%; based on the available data, the FEV1% predicted values were similar between treatment groups.

The reported major lung events of acute rejection, bronchial complications, respiratory failure, major pulmonary infection and re-transplantation were comparable between the EVLP and Control Groups.

UNOS reports on donor lung match runs for lungs treated with EVLP indicate that the XPS™ System increased the utilization rate of initially unacceptable donor lungs.

There was an increase in the utilization of donor lungs with 103 initially unacceptable donor lungs being transplanted into 110 recipients after EVLP. The DCD utilizations and the starting of such programs at NOVEL EVLP centers will likely have an impact on lung allograft availability.

The increase in DCD and low PaO2 donor lung utilization in the EVLP Group was the main contributor for the overall increase in donor lung utilization with a significant impact on donor lung availability.

The transplantability criteria (e.g., post-EVLP) was changed during the course of the NOVEL/NOVEL Extension study but the change did not result in differences in clinical outcomes. Data from before and after the change show comparable survival rates and incidence of PGD Grade 3 at 72 hours post-transplantation. No inferences can be made regarding these criteria as to whether one should be recommended over the other. Also, neither of the criteria have been validated, since the lung function parameters obtained from the XPS™ System have not been validated against parameters obtained prior to the retrieval of lungs from a donor.

B. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in the clinical studies conducted to support PMA approval as described above.

The probable benefits related to the safety and effectiveness of the device are based on data collected in the NOVEL/NOVEL Extension trial and post-hoc analyses using UNOS SRTR registry data and the NIH LTOG dataset as comparators to assess mortality and incidence of PGD.

Even though the NOVEL/NOVEL Extension analysis did not meet the 12% non-inferiority margin for the co-primary endpoints, the post-hoc analyses showed that the XPS™ System presented probable benefit in terms of:

- Comparable survival at 1-, 2- and 3-years post-transplantation between the EVLP Group and matched lungs (i.e., matched by the criteria of the NOVEL/NOVEL Extension study) from the UNOS SRTR registry;
- Comparable PGD Grade 3 at 72 hours post-transplantation performance between the EVLP Arm and the NIH LTOG study;

The NOVEL/NOVEL Extension trial showed the following probable benefits:

- Clinically comparable performance in terms of ICU length of stay, hospital length of stay, duration of mechanical ventilation, delayed extubations, re-intubations and tracheostomies;

- Clinically comparable rates and severity of adverse events, including serious and non-serious MLEs, non-MLE hospitalizations, pneumonias and major pulmonary infections between the EVLP and Control Groups;

- Utilization of previously unacceptable lungs, as evidenced by the lung match runs provided from UNOS, thus increasing the donor pool and the choices available to patients on the waiting list;

- Utilization of DCD donor lungs, which are typically not transplanted in the U.S. and were not previously transplanted in many of the investigational sites of the NOVEL and NOVEL Extension study until the XPS™ System became available via H120003

- Utilization of donor lungs with lower PaO2/Fi02;

- Utilization of donor organs with longer cold ischemia and out-of-body times compared to the control arm;

The probable risks of the device are also based on data collected in the clinical studies conducted to support PMA approval as described above.

The risks are:

- Statistically higher mortality in the EVLP Group compared to the Control Group (all-cause mortality);

- Statistically higher PGD Grade 3 at 72 hours in the EVLP Group compared to the Control Group (when including all ECMO subjects in the analyses).

Additional factors to be considered in determining probable risks and benefits for the XPS™ System with STEEN Solution device included:

- Uncertainties in the use of prophylactic ECMO and its effect on the study's data analyses;

- Uncertainties and potential for selection bias in the conduct of the study pertaining to the enrollment of Control Subjects;

- Uncertainty about adjudication of life time survival analysis (defined as all cause mortality excluding deaths with adjudicated confounding risk factors for mortality);

- High number of missing data in the 2- and 3- year assessments (comparable rates of missing data in the EVLP and Control Arms);

- Missing pulmonary function test data which did not allow for the appropriate evaluation of long-term lung function and BOS;

- Study was not randomized;

- The sample size was too small to adequately assess secondary endpoints;

- There was uncertainly in the data provided by the XPS™ System regarding lung function. Furthermore, it is not clear whether the lung function data provided by the XPS™ System are comparable to data obtained from a donor pre-retrieval for transplant suitability determination purposes, since these parameters have not been validated. A better understanding of the EVLP lung function evaluation will be important and will be evaluated in a post-approval study. The predictive value and relative contribution of the ex-vivo lung function data during EVLP in defining transplantability requires additional understanding and validation.

1. Patient Perspectives

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

In conclusion, given the available information above, the data support that for flushing and temporary continuous normothermic machine perfusion of initially unacceptable excised donor lungs during which time the *ex vivo* function of the lungs can be reassessed for transplantation the probable benefits outweigh the probable risks.

C. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Although the pre-specified primary endpoints were not met statistically, the data from the NOVEL/NOVEL Extension study are clinically relevant and comparable to data from large, real-world registries and studies, such as the UNOS SRTR registry and the LTOG dataset. Also, these findings have to be considered in light of the increased utilization in donor lungs, including the utilization of DCD donor lungs, those with low PaO2, and those with long cold ischemia and out-of-body times.

XIII. CDRH DECISION

CDRH issued an approval order on April 26, 2019. The final conditions of approval cited in the approval order are described below.

Two (2) Post-Approval Studies (PAS) are mandated, as described below. You must provide the following data in post-approval study (PAS) reports for each PAS listed below. Separate PAS Progress Reports must be submitted for each study every six (6) months during the first two (2) years of the study and annually thereafter, unless otherwise specified by FDA. Each report, identified as a "PMA Post-Approval Study

Report" in accordance with how the study is identified below and bearing the applicable PMA reference number, should be submitted to FDA.

PMA Post-Approval Studies:

1. NOVEL/NOVEL Extension Continuation Long-Term Post Approval Study of NOVEL and NOVEL Extension Subjects:

   The NOVEL/NOVEL Extension Continuation Long-Term PAS is a two-arm observational study intended to evaluate long-term outcomes of the NOVEL trial patients. The study population includes all NOVEL and NOVEL Extension patients, including both arms of the study, who consent to participation. The primary effectiveness endpoint is Bronchiolitis Obliterans Syndrome (BOS)-free survival through 5 years after transplantation. The follow-up period for all patients is through 5 years. You are required to have set up this PAS, have collected additional follow up-data on at least 40% of your NOVEL/NOVEL Extension study population for this PAS, and have submitted the initial interim PAS report to FDA within 6 months of PMA approval. By the 1-year interim report, you are required to provide follow-up data on at least 90% of study subjects. You are required to submit a final report to FDA when all patients reach 5-year follow-up, and to have 5-year follow-up data for at least 90% of study subjects.

2. Long-Term Evaluation Post-Approval Study of the XPS™ System with STEEN Solution™ Perfusate:

   The Long-Term Evaluation PAS of the XPS™ System with STEEN Solution™ Perfusate is a prospective, single arm, multi-center study of all comers using the XPS™ System with STEEN Solution™. The study's objectives are to 1) confirm 12-month patient survival data and assess long term performance (i.e., 5 years post-transplantation), 2) assess the effect of the new transplantability criteria (i.e., including the Adaptive Eligibility Criteria introduced in 2014) on lung utilization; and 3) assess real world use of the device with current lung allocation rules. The study will collect data on all donor lungs that are preserved on the XPS™ system and all patients who receive XPS™-treated lungs for 5 years following initiation of the PAS, and includes follow-up for 5 years post-transplantation. The primary endpoint for the study is a composite of 12-month survival and incidence of Primary Graft Dysfunction (PGD) Grade 3 at 72 hours post-transplantation, and these data will be compared to data from the United Network Organ Sharing (UNOS) Scientific Registry of Transplant Recipients (SRTR) registry. The study also assesses, among other things, the incidence of BOS at 1-5 years post-transplantation, Quality of Life at 1-5 years post-transplantation, and patient survival at 1-5 years post-transplantation.

   You will be allowed to continue marketing your device per the approval of HDE120003 for up to 6 months following PMA approval, while the PAS study is being initiated. Within 6 months of PMA approval, you are required to initiate your study, i.e. your FDA-approved PAS clinical protocol and Statistical Analysis Plan

should be in place. Following study initiation, all donor lungs that are preserved on the XPS™ system and all patients who receive XPS™-treated lungs (i.e., all-comers) should be captured in the PAS for the next 5 years. You are required to submit interim PAS reports to FDA as described above. The first interim report should be submitted 6 months after PMA approval. You are required to submit a final report to FDA when all patients reach 5-year follow-up and have 5-year follow-up data on all enrolled study subjects.

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

XIV. 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.

XV. REFERENCES

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