

SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name: Ex Vivo Lung Perfusion (EVLV)

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

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

Date of Panel Recommendation: March 20, 2014

Humanitarian Device Exemption (HDE) Number: H120003

Humanitarian Use Device (HUD) Designation Number: 08-0194

Date of HUD Designation: June 17, 2008

Date of Notice of Approval to Applicant: August 12, 2014

II. INDICATIONS FOR USE

The XVIVO Perfusion System (XPS™) with STEEN Solution™ Perfusate is indicated for the 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 indication for use statement has been modified from that granted for the HUD designation. The HUD designation was granted for the STEEN Solution™ for the indication of “as an aid for *ex vivo* evaluation and perfusion of potential donor lungs prior to possible transplantation.” It was modified for the HDE approval because the HUD designation letter stated that the “approval of a Humanitarian Device Exemption (HDE) would require linkage of the STEEN Solution™ to a device that is approved or cleared to administer/test the solution.” The modified indication for use statement reflects the addition of the required perfusion device.

III. CONTRADICTIONS

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.

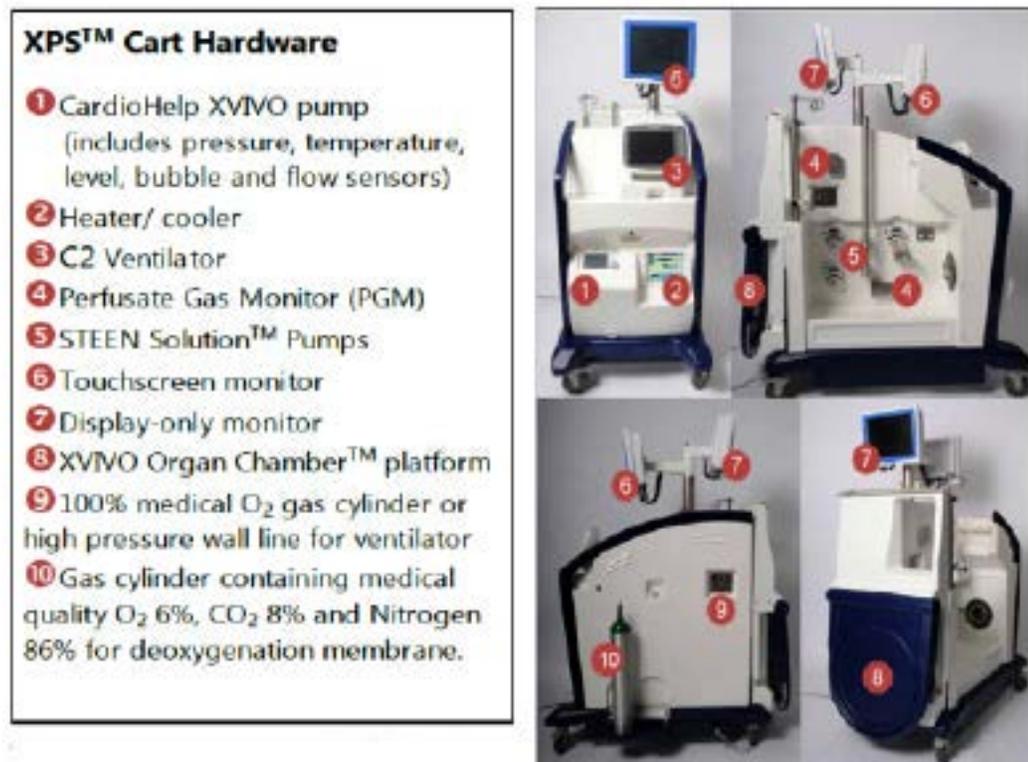


Figure 1 – XVIVO Perfusion System (XPS™)

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 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, PCO₂ (partial pressure of dissolved CO₂), and PO₂ (partial pressure of dissolved O₂). These parameters are displayed in real time to the operator. The PGM has no direct contact with the sterile fluid path. It uses fluorescent 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 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:

- *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% O₂, 8% CO₂, 86% N₂) 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 UPS (uninterruptable power supply) provides battery backup support to the AAEON display and touchscreen monitors and PGMs. The CardioHelp XVIVO and Hamilton C2 ventilator have their own internal battery backups. The Hirtz Variotherm 550 heater/cooler consumes too much power to run on battery, 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 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

Conventional procedures used in the preservation of donor lungs are limited to cold, static storage of the lungs in a hypothermic preservation solution prior to transplantation. 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.

There are no other legally marketed devices in the US that are used for the normothermic flushing and assessment of excised donor lungs *ex vivo*.

VII. MARKETING HISTORY

The XVIVO Perfusion System (XPS™) has not been marketed in the United States; however, the STEEN Solution™ 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. Over 100 EVLP transplants using STEEN Solution™ have been performed in Europe and Australia. STEEN Solution™ 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 reason related to the safety and effectiveness of these devices.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The XPS™ with STEEN Solution™ Perfusate device is indicated for use only on 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 has a direct effect 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.

- Death;
- Renal failure or dysfunction;
- Respiratory dysfunction/infection;
- Primary graft dysfunction;
- Acute rejection;
- Cardiac arrhythmias;
- Bronchiolitis Obliterans Syndrome (BOS)
- Bronchiole stenosis/Dehiscence

IX. SUMMARY OF PRECLINICAL STUDIES

A. Bench Testing Reports

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 1.

Table 1 - 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 <i>In Vitro</i> 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.
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.
<i>In vitro</i> 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 <i>in vitro</i> 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.
<i>In Vitro</i> 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 2 below

Table 2 - 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
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.

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™) was 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 3.

Table 3 – 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
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. Laboratory Testing

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 (EVLVP) 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 4 provides data obtained from the XPS™ software indicating that the various components of the XPS™ system were functioning properly.

Table 4 - Pre-Clinical Results

DATE	Test Subject	CardioHelp Pump	C2 Ventilator	Variotherm HC	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 porcine and one 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 CLINICAL INFORMATION

Data from two (2) clinical trials was considered to support 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 5 - 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 Trial (U.S. Trial): Normothermic EVLP as an Assessment of Extended/Marginal Donor Lungs	n= 31	n= 31

* Cypel M., et al., J Thorac Cardiovasc Surg, 2012¹

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. 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.

Neither the Canadian nor the U.S. clinical studies were powered to show statistical significant differences in the predefined endpoints.

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

a. 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™ (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.⁴ (see Table 10 below).

After four (4) hours of EVLP perfusion, the donor lung was evaluated for a delta $PO_2 > 350$ mmHg and stable pulmonary vascular resistance (PVR), peak airway pressure (pAWp), 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 the HDE, and were also published by different authors at different times, thus the sample sizes in the various analyses are not consistent. 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 lung⁴ (if not ‘standard,’ proceed through EVLP), and recipient match. Upon trial completion, Health Canada permitted ongoing expanded access through compassionate use, resulting in 39 additional EVLP transplants for a total of 61 EVLP transplants.

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.

b. *HELP Trial Results*

1. 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 6). Similarly, Cypel et al., 2012¹ reported that PGD Grade 3 at 72 hours was 2% and 8.5% in the EVLP and control arms, respectively (see Table 7).

Table 6 - PGD Grades, HELP Trial

Toronto General Hospital Patients-PGD						
PGD Grade	Controls N=103			EVLP N=35		
	T 0hr	T 24hrs	T 72hrs	T 0hr	T24hrs	T72hrs
1	72	55	63	25	28	30
2	16	33	24	5	5	4
3	15	9	11	5	2	1
No Value Obtained	0	6	5	0	0	0

Note: Extubated patients were not given a PGD score

Table 7 - Recipient Outcomes in *ex vivo* Lung Perfusion, HELP Trial

Variable	EVLP (n = 50)	Controls (n = 253)	P value
PGD 3 at 72 h (%)	2	8.5	.14
ECLS (%)	2	2.7	1.00
Mechanical ventilation (d)			.30
Median	2	2.2	
Range	1-101	1-43	
ICU stay (d)			.32
Median	4	4.5	
Range	1-100	1-257	
Hospital stay (d)			.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*, intensive care unit.

Source: Table obtained from Cypel *et. al.*, 2012¹, includes “compassionate extension.”

Controls: Standard static cold storage.

2. Survival Analyses

Thirty-day mortality was reported as 4% and 3.5% for the EVLP and control arms, respectively (p=1.0) (see Table 7). Table 8 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 two (2) 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, possibly because only 28 had reached that time point when the analysis was performed. It is unclear what the status of the remaining 33 patients is (see Table 8). Finally, since the data were obtained from the sponsor’s HDE application, as well as from the cited publications, there are some discrepancies in the patient numbers, since different analyses included different sample sizes.

Table 8 - 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 9 below.

Table 9 - HELP Survival (last follow up – May 24, 2013*)

Toronto General Hospital Patients-Survival		
	Control N=397	EVLP N=74
Alive	309	57
Expired	88	17
Survival Days (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 2010². 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.*, 2012¹.

3. 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 the HDE included only the highest predicted FEV1 (%) on double lung transplants (Table 8).

B. U.S. NOVEL Trial (Normothermic EVLP as an Assessment of Extended/Marginal Donor Lungs, N=31 EVLP and 31 Control Transplants)

This is a prospective, controlled, multicenter, open label, non-inferiority study, including patients transplanted with “extended criteria donor lungs,” that were initially considered unacceptable for transplantation.

Unacceptable donor lungs were defined as those not meeting the clinical donor lung criteria, based on the 2003 ISHLT consensus document on lung transplant acceptability criteria⁴ (see Table 10), and compared to a selected control group of standard, cold storage lung transplant recipients performed during the same period of time, at the same investigational sites.

Table 10 - Donor Lung Selection Criteria

Ideal donor lung criteria, 2003 ISHLT consensus	“Acceptable” donor lung selection criteria in 2012 ⁶
<ol style="list-style-type: none"> 1. Age < 55 years 2. ABO blood group compatible 3. Clear chest radiograph 4. PaO₂:FiO₂ > 300 on FiO₂=1 and 5 cm H₂O positive end expiratory pressure 5. Tobacco history < 20 pack-years 6. Absence of chest trauma 7. No evidence of aspiration or sepsis 8. Absence of purulent secretions at bronchoscopy 9. Absence of organisms on sputum Gram stain 10. No prior cardiopulmonary surgery 11. Donation after brain death donor (DBD) 12. Appropriate size match 13. No history of primary pulmonary disease or active pulmonary infection 	<ol style="list-style-type: none"> 1. Age < 70 years 2. ABO blood group compatible 3. Donation after brain death (DBD) or donation after cardiac death donor (DCD) 4. Approximate size match with minor surgical trimming or lobectomy as needed 5. Minor diffuse and moderate focal chest radiographic changes acceptable if good, stable/improving function. 6. PaO₂:FiO₂ > 250 on 5 cm H₂O positive end-expiratory pressure 7. Tobacco history < 40 pack-years 8. Chest trauma not relevant if good function 9. Aspiration or minor sepsis acceptable if good, stable/improving function 10. Purulent secretions not relevant if good, stable/improving function 11. Organisms on Gram stain and ventilation time not relevant 12. Primary donor pulmonary disease not acceptable, unless asthma 13. Lungs deemed initially unacceptable but are resuscitated with ex vivo lung perfusion

Source: Adapted from Van Raemdonck *et.al.*⁸, Snell *et.al.*⁶, Sundaesan *et. al.*⁷, and Orens *et.al.*⁴

The NOVEL trial is an ongoing study conducted in five (5) centers in the U.S. that was started in May, 2011. The HDE submission included 61 patients (31 EVLP and 31 control subjects).

The primary outcome for this study was 30 day mortality; however, the NOVEL study was not powered to demonstrate statistical differences across study groups for the endpoints.

In this trial, lung donors had to meet pre-EVLP inclusion/exclusion criteria to be eligible for the EVLP procedure. During the EVLP procedure, the lungs were evaluated every hour to assess functional improvement. The lungs then had to meet post-EVLP criteria to determine if they were suitable for transplant. If eligible, they were transplanted into a recipient in the EVLP treatment arm. The research centers enrolled controls based on the EVLP enrollment to permit equal distribution of subjects between treatment arms across all centers.

Donors in the Study and Control Populations

Donor lungs not meeting the ideal clinical donor lung criteria, based on the 2003 ISHLT consensus document on lung transplant acceptability criteria⁴, and rejected by other transplant centers for ‘quality’ reasons were evaluated for the EVLP arm. Donor lungs were included in the EVLP arm if at the time of the clinical evaluation,

the donor PaO₂/FiO₂ was ≤ 300mmHg; or if the PaO₂/FiO₂ was > 300 mmHg and one or more of the following donor risk factors were present.

Donor Risk Factors:

- Multiple blood transfusions;
- Pulmonary edema detected via Chest x-ray, bronchoscopy or palpation of lungs;
- Donation after cardiac death donors (DCD);
- Investigator evaluation of donor lung as “unsuitable” for standard criteria for lung transplant.

The control group included recipients of standard, cold storage lung transplants, performed during the same period of time, at the same investigational sites.

Donors were excluded from both groups if they had significant pneumonia or persistent purulent secretions, aspirated gastric contents in to the lung, significant lung trauma, or active infectious disease such as human immunodeficiency virus (HIV), hepatitis B or C, human T-lymphotropic viruses (HTLV), or syphilis.

Recipient Population

The NOVEL trial was designed as a two-treatment arm study for any patient requiring a lung transplant to receive either an EVLP-perfused lung or a standard, non-EVLP perfused lung (control) working within the established United Network for Organ Sharing (UNOS) allocation policies. Additionally, the recipient must have been consented into the study, could not be on any mechanical ventilation, had not received a prior lung transplant (same side), and could not have any active infectious diseases. The NOVEL trial was not intended to provide EVLP-perfused organs to the sickest recipients in the waiting list. Donor lungs were allocated following current standard UNOS allocation rules and were assigned to the EVLP or CS groups, based on the study inclusion/exclusion criteria.

NOVEL Trial Results

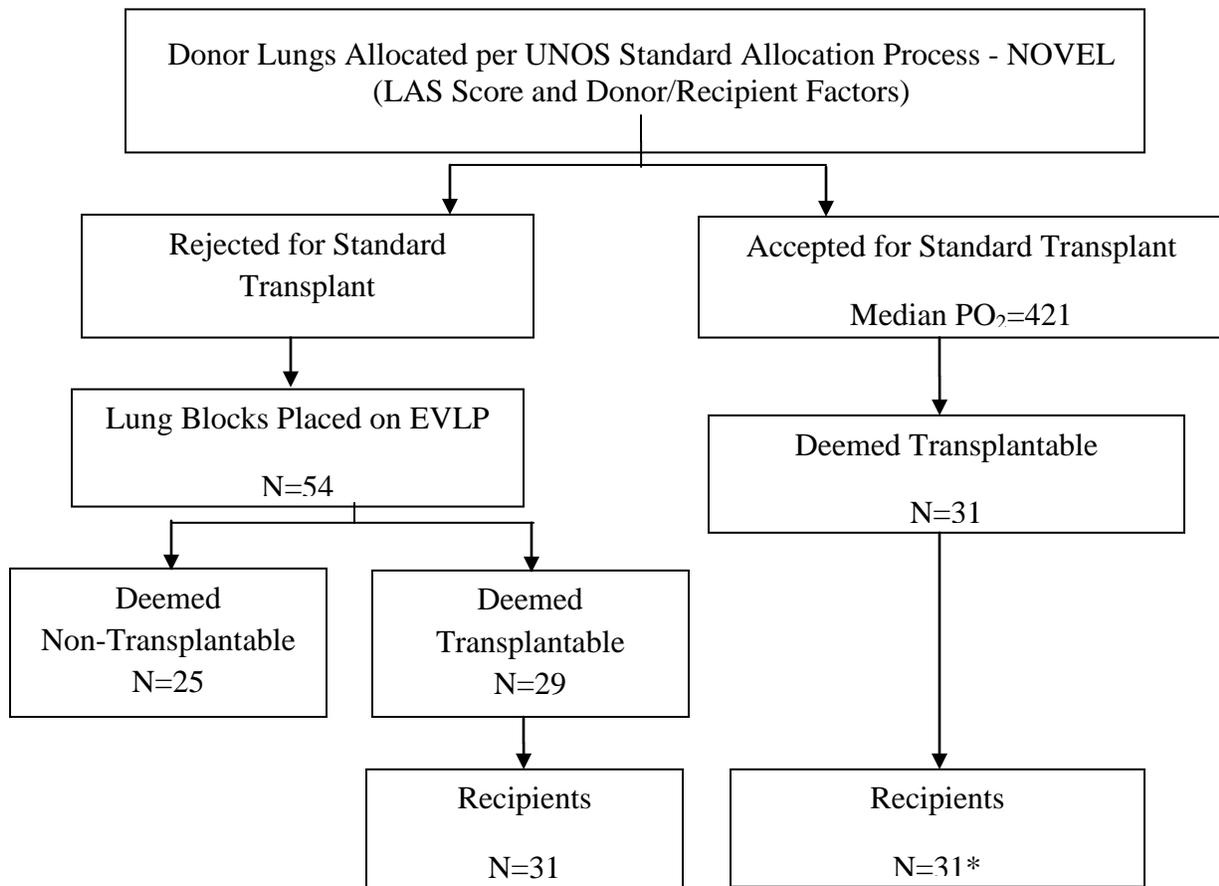
Fifty four (54) lung donors met the criteria and underwent EVLP. From this group 29 (54%) were transplanted into 31 recipients. Fifteen (15) recipients received double lung transplants and 16 recipients received single lung transplants, with 12 single lungs discarded. Additionally, 25 donor lungs or lung pairs (46%) were discarded after EVLP and not transplanted. For the control group, 50 standard criteria lungs were transplanted into 31 recipients, with 19 (61%) receiving double lung transplants and 12 (39%) receiving single lung transplants.

Table 11 - Disposition of Lungs Enrolled into the NOVEL Study

STUDY GROUPS By Preservation Method	Cold Storage (Conventional)		EVLP-Transplanted (Tx)		EVLP-Not- Transplanted (Not-Tx)
	DLTx	SLTx	DLTx	SLTx	
DONORS (Number of lungs)	31 (50)		29 (47)		25 (43)
RECIPIENTS	31		31		n/a
Recipients per Transplant Type (%)	DLTx 19 (61%)	SLTx 12 (39%)	DLTx 15 (48%)	SLTx 16 (52%)	n/a
Single Lungs Discards	0	12	1	0	n/a ⁷
Double Lungs Discards	0	-	0	-	18

CS = Cold Storage, DLTx = Double Lung Transplant, SLTx = Single Lung Transplant

Figure 3 – Donor Lung Allocation for NOVEL Trial



* Next available conventional transplants enrolled after EVLP transplants

Donors Baseline Characteristics in the Novel Trial.

The donors' baseline characteristics are described in the Tables 12 and 13.

Table 12 - Donors Baseline Characteristics

Donors data	Cold Storage controls n=31	EVLP- Tx n=29	EVLP-Not-Tx n=25
Donor Type			
BDD	30 (97%)	27 (93%)	20 (80%)
DCD	1 (3%)	2 (7%)	5 (20%)
Donor Gender M/F	21/10	17/12	13/12
Age			
≤ 54	27 (87%)	27 (93%)	23 (92%)
55 – 59	1 (3%)	0	0
60+	3 (10%)	2 (7%)	0
Median years (range)	37 (19-70)	31(16-65)	28 (13-48)
Best PaO₂ Median (Range)	421 (285-589)	348 (165-500)	333 (119-501)
CMV+	16 (52%)	10 (34%)	13 (48%)
Bal + Cultures	13 (42%)	12 (41%)	9 (36%)
Smoking History			
Positive	13 (42%)	13 (45%)	9 (36%)
Negative or NA	18 (58%)	16 (55%)	15 (60%)
Cause of death			
Anoxia / Hypoxia	10 (32%)	12 (41%)	6 (24%)
Trauma	11 (35%)	14 (48%)	11 (44%)
CVA/Stroke	10 (32%)	3 (10%)	8 (32%)
Partial pressure of arterial oxygen / Fraction of inspired oxygen (PaO₂ / FiO₂)			
>350	26 (84%)	12 (41%)*	11 (44%)
301-350 & NA	3 (10%)	12 (41%)**	4 (16%)
≤ 300	2 (6%)	5(17%)***	10 (40%)

^ Donor last PO₂ / FiO₂ before organ retrieval

* Transplanted as 5 SLTx and 7 DLTx

** Transplanted as 6 SLTx and 7 DLTx

*** Transplanted as 5 SLTx and 1 DLTx

Most of the donor characteristics were similar across the EVLP and control groups. Donors with history of malignancy, sepsis, drug abuse, and meningitis were excluded from the study. Smoking history was equally distributed among groups and the proportion of donors with low PaO₂/FiO₂ was 6% and 17% in the control and EVLP arms, respectively. The difference in PaO₂ /FiO₂, with lower values in the EVLP group, is expected because of the inclusion/exclusion criteria. Donor

lung scores were not calculated by the applicant, since that parameter was not included in the clinical protocol.

Table 13 - Donor Evaluation: Donor lungs considered unacceptable for transplantation and accepted for EVLP preservation and evaluation

Donor Evaluation	Donor lungs considered unacceptable for transplantation and accepted for EVLP preservation and evaluation n=54		
	Total n=54	Transplanted after EVLP	Not- transplanted after EVLP
Pulmonary edema + lungs boggy	32/54 (59%)	20/32 (62.5%)	12/32 (37.5%)
PaO ₂ less than 300	15/54 (28%)**	5/15 (33%)	10/15 (67%)
Donation after cardiac death (DCD)	7	2	5
Infiltrates	6	4	2
Contusions	5	5	0
Infarction only	1	-	-
Multiple blood transfusions	4	2	2
Asphyxiation / Donor hanged	2	1	1
Drowning donor		1	1

* Donor may present more than one cause for non-acceptance. 73 causes for non-acceptance were listed for 54 donors.

** There were two (2) DCD that also presented PaO₂ < 300. These two (2) donors were included in the DCD category, and excluded from the PaO₂ < 300 mm Hg category.

Of the 25 EVLP not transplanted, 10 presented a PaO₂ < 300 mm Hg, and the other 15 presented a PaO₂ > 300 mm Hg with another reason for not being transplanted (including surgeon not satisfied). Other reasons why the lungs were not transplanted are listed in Table 13.

Determination of Unacceptable Donor Lungs that qualified for EVLP

During the study period, 54 donor lungs pairs met the inclusion and exclusion criteria for EVLP.

In addition, these 54 donor lung pairs were not accepted for transplantation by a non-EVLP center because of organ quality issues. Fifteen (15) donors met the criterion of PaO₂/FiO₂ < 300 mm Hg. The other 39 donors had PaO₂/FiO₂ > 300

mm Hg and other alternative reasons for non-acceptance. The lung donors presented one or more causes for non-acceptance; 73 causes for non-acceptance were listed for 54 donors (see Table 13 above).

The leading reason for non-acceptance of the donor lungs for transplantation was pulmonary edema in 59% (32/54), followed by $\text{PaO}_2 < 300$ mm Hg in 28% (15/54) of the EVLP cases. Pulmonary edema as a single reason for considering the donor lungs unacceptable was found in (16/32) 50% of the donors. The other 16 donors presented pulmonary edema in combination with infiltrates, contusions, or multiple blood transfusions.

After the EVLP procedure, 25 EVLP donor lung pairs were not transplanted and 29 EVLP donor lung pairs were transplanted across 31 recipients (see Table 13).

Donor Lungs Transplanted and Not Transplanted after EVLP

After EVLP, 29 out of 54 (54%) donor lung pairs were transplanted across 31 recipients (EVLP utilization rate of 54%) and 25 out of 54 (46%) donor lung pairs were not transplanted.

Fifteen (15) donor lung pairs underwent EVLP because their $\text{PaO}_2/\text{FiO}_2$ was less than 300 mm Hg. Only five (5) of them (33%) were subsequently transplanted. The other 39 donor lung pairs that underwent EVLP had $\text{PaO}_2/\text{FiO}_2 > 300$ mm Hg and other alternative reasons for non-acceptance (11 pulmonary edema/infiltrates/multiple blood transfusions, 2 infarcts/unable to perform bronchoscopy, and 2 DCDs). Twenty-four (24) out of 39 of them (62%) were subsequently transplanted. Donor lungs with edema alone or in combination with infiltrates, contusions, or multiple blood transfusions before EVLP were transplanted after EVLP in 62% (20/32) of cases.

The main reason for donor lung initial non-acceptance and subsequent non-transplantation after EVLP was donation after cardiac death (DCD). Seven (7) DCD donor lungs were considered unacceptable for transplantation prior to EVLP. After EVLP, two (2) of them were accepted for transplant and five (5) remained unacceptable (see Table 13).

EVLP Transplantability Lung Function Evaluation

Table 14 lists the major reasons for not transplanting lungs after EVLP evaluation.

Table 14 - Major Reasons for not Transplanting Lungs after EVLP

Major Reasons For Rejection After EVLP	N
Pulmonary Edema	16
Increased Pulmonary Vascular Resistance (PVR)	10
Decreased Compliance	11
Airway Pressures	5
Low Delta P _{O₂} /FiO ₂	18
Fluid Level in Reservoir Decreasing (edematous lungs)	3
Logistics	1

Note: The term “Rejection” used in the table indicates non-acceptance for transplantation. It does not refer to immunological allograft rejection.

UNOS Report on the Donor Lung Match Runs

One of the ways to determine probable benefit in this study was to show that with the EVLP method useable lungs could safely be added to the donor pool.

XVIVO Perfusion, Inc. provided a custom UNOS report on the donors of lungs used for EVLP in the NOVEL trial. The report included data on 51 donor lungs that underwent EVLP and these data are summarized in Table 15. All lungs offered and ultimately accepted by an EVLP trial center were rejected by at least one other non-EVLP transplant center due to poor lung “quality.”

Table 15 - UNOS Donor Lung Match Runs for the NOVEL EVLP Lungs

Recipient Match attempts by OPO		
	Transplanted	Not transplanted
EVLP lungs n=54*	29 donor for 31 transplants*	25 donors*
Lung match runs, n	28	23
Mean	62	52
Median	39.5	28
Recipient match sequence**		
Recipient's position on the waiting list**		
1 & 2	5/28 (18%)	
≤ 3	6/28 (21%)	
≤5	8/28 (29 %)	
≤10	13/28 (46%)	
>10	15/28 (54%), Range (11-296)	

* Indicates if lungs were refused by other transplant centers due to poor quality.

** The recipient match sequence indicates the recipient's position on the Donor Net list

Note: Information summarized in the table above is based on data as of April 26, 2013. These data were provided by TII, a subsidiary of UNOS, as requested by XVIVO Perfusion, Inc.

On average, a total of 65 refusals were received before and after the study center accepted the organs for EVLP. An average of 24 refusals was received before acceptance for EVLP.

Rescuing initially rejected donor lungs is a clear benefit, when these lungs can provide acceptable short and long term clinical outcomes.

Recipient Population

Table 16 - Recipient Characteristics

Recipient Data	EVLP (n=31)	Control (n=31)
Age Median (range)	63 (31-77)	59 (37-72)
M/F	20/11	16/15
Diagnosis		
IPF	17	8
COPD/Emphysema	11	13
PPH	1	3
Cystic Fibrosis	1	3
Bronchiectasis	1	0
Scleroderma	0	1
A1T1	0	2
LAM	0	1
CVM(+)	18	14
LAS Score Median (range)	40 (31-95)	37 (28-72)

Most of the recipient characteristics were similar across the EVLP and control groups. The difference in PaO₂ /FiO₂, with higher values in the control group, is expected because of the inclusion criteria for EVLP.

There were more cerebrovascular accident (CVA) /stroke donors in the control, cold storage group, and more broncheoalveolar lavage (BAL) positive culture in the EVLP group.

There were differences in the number of recipients with Idiopathic Pulmonary Fibrosis (IPF) as leading cause for lung transplantation, 17 *versus* 8 in the EVLP and control groups, respectively. This difference was analyzed and demonstrated that it did not increase mortality in the EVLP arm. One-year survival rates were 76%, 75%, and 74% for the control, EVLP, and ISHLT registry, respectively (see Figure 4).

Figure 4 - Kaplan-Meier Survival Adjusted for Idiopathic Pulmonary Fibrosis (IPF) Recipients

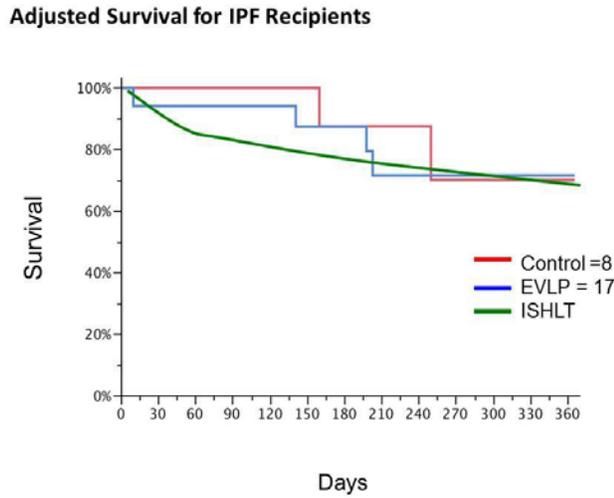


Table 17 below shows the recipient lung allocation scores (LAS) at transplant for the NOVEL study.

Table 17 - Lung Allocation Score at Transplant by Lower, Mid and High Priority

	CS-Conventional (n=31)		EVLP-Tx (n=31)		EVLP-Not-Tx (n=25)
	BLTx n=19	SLTx n=12	BLTx n=15	SLTx n=16 (Sp 4)	N/A
LAS at Transplant					
Lower priority	(90%)		(81%)		
<40	15	7	8	9	
40-49	3	3	2	6	
Mid priority	(10%)		(13%)		
50-59	1	1	1	1	
60-69	0	1	1	0	
70-79	0	0	1	0	
High priority	(0%)		(6%)		
89-89	0	0	0	0	
90+	0	0	2	0	

The majority of the recipients (90% and 81% in the control and EVLP arms, respectively) were in the lower priority strata (LAS ≤ 49). According to Russo et al.⁵, in the lowest-priority strata (i.e., <40 and 40–49), less than 4% of candidates died on the waiting list within 90 days of listing. In his analyses, Russo found that

the median net survival benefit was the lowest among the lung allocation scores of less than 40 (i.e., - 0.7 years).

All the above mentioned recipient differences across arms were difficult to interpret in this small study. The observed differences in the number of recipients with IPF as leading cause for lung transplantation (e.g., 17 *versus* 8 in the EVLP and control groups, respectively), did not show a detrimental effect on survival (see Figure 3), nor an effect on outcomes. Therefore, caution should be taken when assessing these differences.

EVLP Transplantability Criteria and Protocol Deviations

The NOVEL protocol required that the EVLP lungs meet all the transplant suitability criteria to consider the EVLP donor lungs adequate for transplantation after EVLP. Patients that failed one or more criteria were supposed to be excluded from transplantation.

Table 18 below shows the number of patients that either met or did not meet the EVLP transplantability criteria after EVLP, including those who did not meet the criteria and still were transplanted (i.e., protocol deviations). The data also show that some EVLP donor lungs were not transplanted despite meeting the EVLP transplantability criteria (e.g., surgeon not satisfied).

Table 18 - EVLP Transplantability Criteria and Protocol Deviations

EVLP Lung Pairs (n=54) Transplant Suitability Criteria*	EVLP-Tx (n=29)		EVLP Not-Tx (n=25) Did not meet criteria
	Met Criteria n=12	Did not meet criteria, (Protocol Deviations)** n=17 (59%)	
1. Delta PaO₂ > 350 mmHg at two times during EVLP	16 (55%)	13 (45%)	7 (28%)
2. Improvement or Stability (≤10% deterioration), n (%)			
• Pulmonary vascular resistance	26 (90%)	3 (10%)	15 (60%)
• Compliance	27 (93%)	2 (7%)	20 (80%)
• Peak airway pressure (Pawp)	24 (83%)	5 (17%)	20 (80%)
3. Surgeon satisfied with lung evaluation	100%	100%	-

* The EVLP lungs were to meet all the transplantability criteria to be considered suitable for transplantation. In other words, patients that failed one criterion were supposed to be excluded from transplantation. In addition, surgeon satisfaction was also required.

** EVLP lungs may have failed to meet more than one criterion for transplantability.

Low delta PaO₂ was the most common reason to reject lungs for transplantation after EVLP. The delta PaO₂ criterion for transplantability was met in 55% of the donor lungs transplanted after EVLP.

Improvement or stability in lung function parameters during EVLP (≤10% deterioration) was met in 90%, 93%, and 83% of the transplanted lungs after EVLP, for PVR, lung compliance, and PawP, respectively (see Table 18).

EVLP donor lungs not meeting the pre-specified delta PaO₂ criterion and still being transplanted was the most frequent cause of protocol deviations. Seventeen (17) protocol deviations related to the EVLP transplantability criteria (i.e., patients that did not meet the criteria and still were transplanted) were reported. This corresponds to 59% of the EVLP-transplanted lungs (See Table 19). Among the 17 EVLP protocol deviations, there were three (3) recipients that presented PGD Grade 3 at 72 hours and five (5) recipients died.

From these results, it is challenging to define the relative contribution of the pre-specified EVLP transplantability criteria to determine which donor lungs should be transplanted after EVLP (i.e., which donor lungs will perform well after transplantation (e.g., absence of PGD Grade 3 at 72 hrs)). Furthermore, it is not clear whether the lung function data provided by the XPS™ System is comparable or better, to data obtained from a donor pre-explant for transplant suitability determination purposes.

The Advisory Panel that reviewed the XPS™ System with STEEN Solution™ Perfusate was asked to comment on the EVLP lung function evaluations performed and whether the pre-specified transplantability criteria are appropriate to inform the labeling of the device. The panel unanimously agreed that a better understanding of these parameters is required, but that they should remain as part of the treatment and the device. Panelist stated that this issue should be addressed in the Post Approval Study (PAS) or PMA studies.

Table 19 - Protocol Deviation Listings*

Site	Subject	Deviation	Period 1 (Delta PaO2)	Period 2 (Delta PaO2)
03-Brigham	0301	Post EVLP- One delta PaO2 was not greater than 350 mmHg.	320.2 pvO2 397	380.9 pvO2 464.5
04-Colorado	0402	Post EVLP- One delta PaO2 was not greater than 350 mmHg.- not a true deviation after conversion due to Colorado altitude difference. Converted Delta PaO2 Time period 1: 412 Time period 2: 350	338 pvO2 418	287 pvO2 370
04-Colorado	0402	EVLP run ended at 2 hrs and 45 minutes (needed to end at 3 hrs if transplant suitable) therefore second EVLP chest xray was not done		
04-Colorado	0404	Post EVLP- One delta PaO2 was not greater than 350 mmHg. Converted Delta PaO2 Time period 1: 279 Time period 2: 377	229 pvO2 378	309 pvO2 389
04-Colorado	0406	Post EVLP- Two delta PaO2 was not greater than 350 mmHg. Converted Delta PaO2 Time period 1: 318 Time period 2: 328	261 pvO2 340	269 pvO2 351
04-Colorado	0409	Post EVLP- One delta PaO2 was not greater than 350 mmHg. - not a true deviation after conversion due to Colorado altitude difference. Converted Delta PaO2 Time period 1: 390 Time period 2: 418	320 pvO2 399	343 pvO2 422
04-Colorado	0412	Post EVLP- One delta PaO2 was not greater than 350 mmHg. - not a true deviation after conversion due to Colorado altitude difference. Converted Delta PaO2 Time period 1: 385 Time period 2: 367	316 pvO2 395	301 pvO2 375
05-Duke	0502	Post EVLP- One delta PaO2 was not greater than 350 mmHg.	391 pvO2 521	280 pvO2 450
05-Duke	0503	Post EVLP- Both delta PaO2 was not greater than 350 mmHg.	215 pvO2 479	221 pvO2 540
05-Duke	0513/0514	Post EVLP- Both delta PaO2 was not greater than 350 mmHg.	269 pvO2 377	335 pvO2 409
05-Duke	0513/0514	EVLP perfusion extended to 5 hrs and 45 minutes.		
05-Duke	0527	Subject visit occurred one day out of window.		
06-Penn	0602	Post EVLP- Both delta PaO2 was not greater than 350 mmHg. - center notified sponsor for approval prior to transplant based on all parameters improving and PO2 at 400.	344 pvO2 452	326.7 pvO2 422

* The table does not include information on the rationale for the transplant surgeons to transplant EVLP lungs that did not meet the pre-specified transplantability criteria. (59% of the EVLP transplanted lungs).

Note: PvO₂ was not a parameter included as transplantability criteria.

The Advisory Panel was aware of the protocol deviations observed during the study and acknowledged the difficulties of using the lung function data provided by the XPS™ System in making a transplantability decision.

Cold Ischemia Time

Table 20 - EVLP Preservation Parameters and Cold Ischemia Times (CIT)

Donor Data	EVLP Transplanted (n=25)	Cold Storage (n=31)
CIT 1st Ischemic Period (min) Median (Range) Mean (SD)	214 (70-352) 204 (±74)	286 (114-602) 306 (±114)
CIT 2nd Ischemic Period (min) Median (Range) Mean (SD)	258 (56-517) 271 (±125)	
EVLP Time (min) Median	220	N/A
Total Out of Body Time (min) Median	692	286

Mean cold ischemia time (CIT) was higher in the EVLP group (475 min) as compared to the CIT in the control group (306 min) (see Table 20). Likewise, the total preservation time was higher in the EVLP group compared to the control group (median of 692 min vs. 286 min, respectively). Despite these differences, the short-term outcomes (i.e., 30-day mortality and PGD) were comparable across the study groups, as discussed below.

Primary Endpoint

The primary endpoint of the NOVEL trial is a 30-day survival comparison between the EVLP and Control (cold storage) arms. The study was underpowered for this endpoint. Thirty-day survival in both the EVLP and control groups was similar to the ISHLT registry data (see Table 21 below).

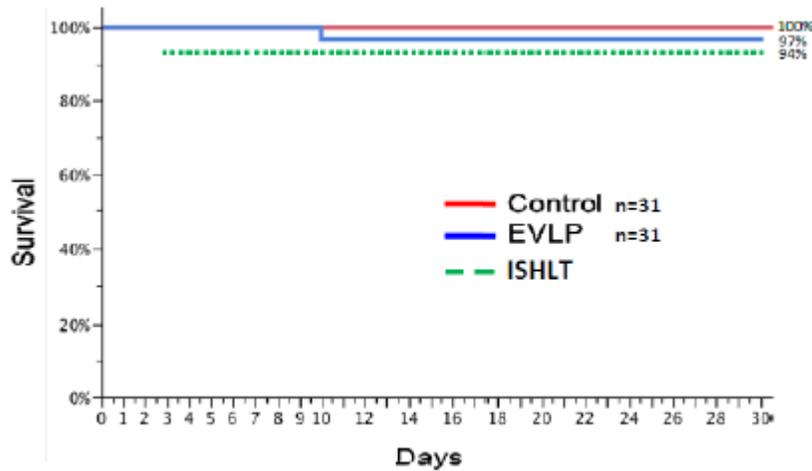
Table 21 – NOVEL Study 30-day Survival

Group	30 Day Patient Survival
EVLP Transplant	97% (n=31)
Control Transplant	100% (n=31)
ISHLT Registry Reference*	94%

* Thirty-day survival, as reported by the International Society of Heart and Lung Transplantations (ISHLT) Registry, is 94% for all lung transplants in their registry database (n=17,715 from 2004 -2010). The overall 30-day survival for NOVEL Trial lung recipients receiving a lung after EVLP was 97%.

The Kaplan-Meier Survival curve, plotted below, shows that for the two (2) groups of transplanted patients, EVLP vs. standard cold storage controls, there is no difference for 30 day survival. The study was not powered to demonstrate differences in 30-day survival across study groups.

Figure 5 - 30 day Survival – EVLP vs. Control



Secondary Endpoints

Secondary endpoints in the NOVEL trial include the following post-transplant data points: PGD at 24 and 72 hours; Extracorporeal Life Support (ECLS)/ Extracorporeal Membrane Oxygenation (ECMO); mechanical ventilation days; ICU stay days; hospital stay days, and one-year survival status.

Pulmonary Function Tests (PTF) were not included as endpoints in the protocol; however, data on PFT's were collected retrospectively at the request of FDA.

Table 22 – Secondary Endpoints

Lung Tx Outcomes	ISHLT Reference Data	EVLP Tx (n=31)	Control (n=31)
PGD			
24 hrs			
2	18%	8 (26%)	5 (16%)
3	28%	5 (16%)	2 (6%)
72 hrs			
2	11%	3 (10%)	4 (13%)
3	18%	3 (10%)	1 (3%)
Patients ECLS post Tx	n/a	2* (6%)	1 (3%)
# Days		5	4
Mech Ventilation Days Median (Range)	n/a	1 (1-196)	1 (1-29)
ICU Stay Days Median (Range)	n/a	4 (1-197)	3 (1-144)
Hospital Stay Days Median (Range)	n/a	13 (4-198)	11 (6-236)
1 Year Survival %	83%	88%	94%

The incidence of PGD Grade 3 at 72 hours was 10% and 3% in the EVLP and control groups, respectively. The study was not powered to show differences in PGD.

The ICU and hospital lengths of stay showed no significant differences between the two (2) treatment groups.

Figure 6 compares the NOVEL study EVLP and control groups using a Kaplan-Meier Long-Term Survival Curve. It should be noted that this graph is not adjusted for diagnosis.

Figure 6 - Long-Term Survival

NOVEL Long-Term Survival (Unadjusted)

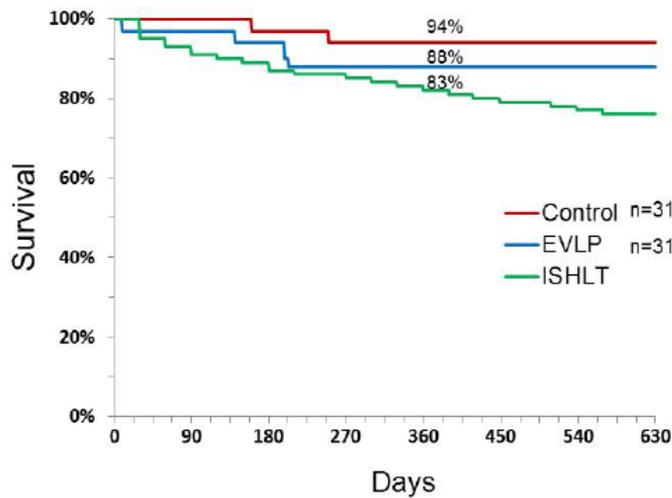


Figure 10- 7 Kaplan-Meier Long-term Survival EVLP vs. Control

The analysis does not specify how many patients were included at each time point and how many patients reached the 630-day post-transplant point in the control and study groups. The Advisory Panel recommended long-term (e.g., 3-year) follow-up as a minimum for long term evaluation in the post-market setting.

Deaths

Table 23 lists the causes for the deaths that occurred in the NOVEL Trial.

Table 23 – Mortality Summary, NOVEL Study

Tx Arm	Donor Type	Recipient Dx	PGD at 72 Hrs	LAS	Hospital Stay (Days)	Survival (Days)	Cause
Control	BD	IPF	0	47	10	160	Airway Stenosis Respiratory Failure
Control	BD	IPF	2	39	250	250	Renal Failure
EVLP	BD	IPF	3	32	10	10	Reperfusion injury /diffuse alveolar hemorrhage due to Cytokine Release Syndrome associated to Thymoglobuline use
EVLP	BD	IPF	2*	49	13	141	Acute Rejection Respiratory Failure
EVLP	DCD	IPF	3	43	198	198	Complications from Aortic Injury
EVLP	BD	IPF	1	71	67	203	Airway Stenosis
EVLP	BD	COPD	0	33	13	272	Leukemia resulting in Bronchiolitis Obliterans Syndrome

Seven (7) deaths were observed in the NOVEL study: five (5) occurred in the EVLP group and two (2) in the CS control group. The seventh death in the study (i.e., fifth EVLP death) occurred on June 11, 2013, after the data were locked down for analysis; however, it is discussed here for completeness. The survival time listed for this subject was 272 days.

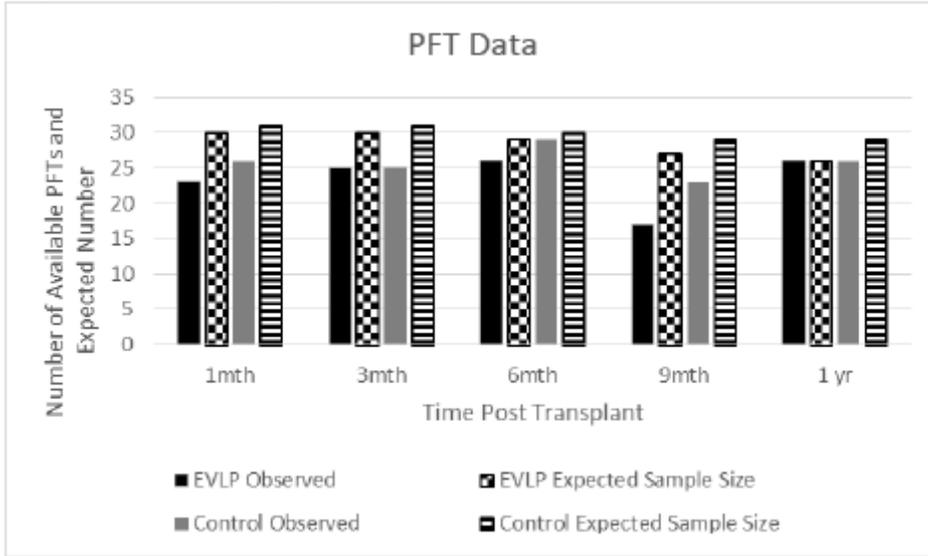
One (1) early death occurred in the EVLP group at post-operative Day 10. That recipient had a low LAS of 32 and the cause of death was attributed to “Reperfusion injury due to Cytokine Release Syndrome” in a patient receiving thymoglobulin. The other six (6) deaths occurred beyond the fourth month after transplantation.

The five (5) EVLP deaths occurred in protocol deviation cases in which lungs did not meet the transplantability criteria, but were transplanted (after correction of PaO₂ delta for high altitude, three (3) of five (5) met the PaO₂ criterion). All five (5) EVLP deaths were determined to be unrelated to the EVLP procedure, both by the investigators and by the safety review committee.

Pulmonary Function Tests

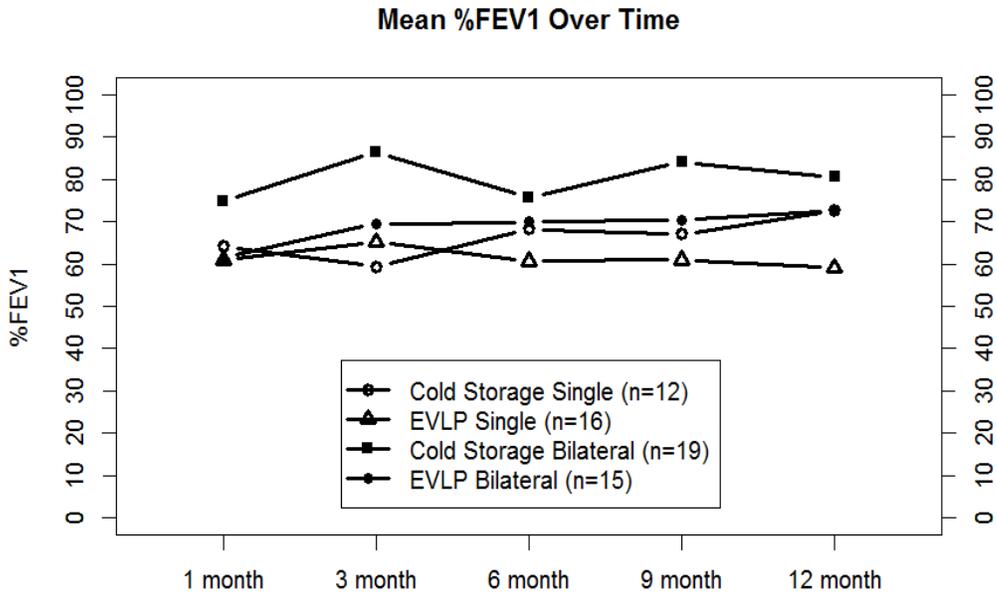
The NOVEL study was not designed to collect or analyze PFTs; however, the applicant collected PFT data retrospectively at FDA's request. These data are presented in Figures 7, 8, and -9, below.

Figure 7 - Pulmonary Function Test (PFT) Evaluations



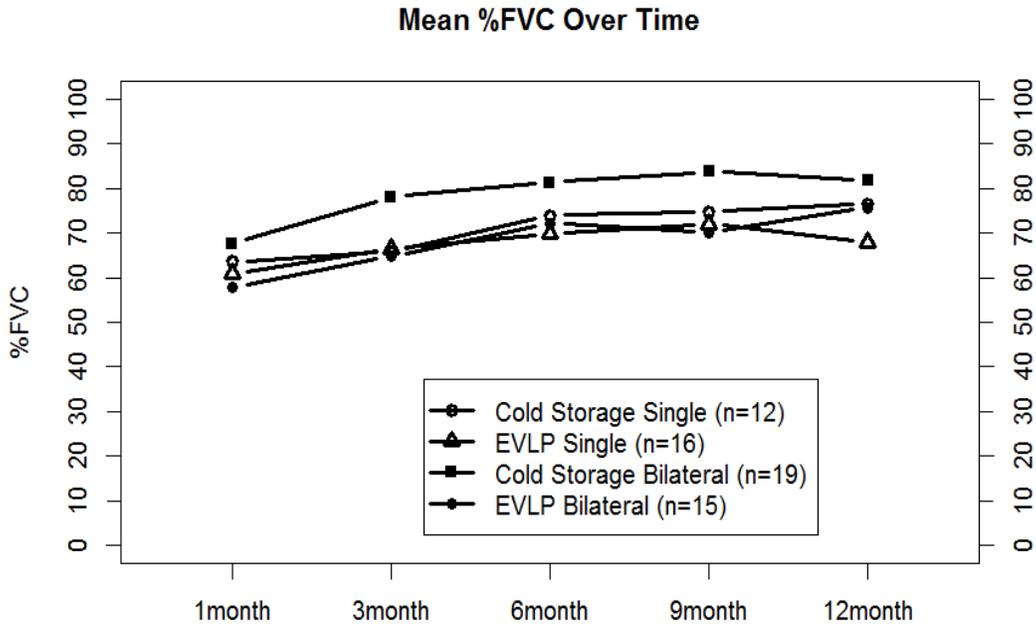
PFT evaluations were observed in 80% or more of patients at the various time points in both the EVLP and control arms.

Figure 8 - Mean Changes in % FEV1 Over Time



At 12 months after transplantation, the mean % FEV1 was 80.47 vs. 72.45 for cold storage vs. EVLP double lung transplants, respectively. In the single lung transplant arms, the mean % FEV1 was 72.64 vs. 59.07 for the cold storage vs. EVLP groups, respectively.

Figure 9 - Mean Changes in %FVC Over Time



At 12 months after transplantation, the mean %FVC was 81.67 vs. 75.64 for cold storage vs. EVLP double lung transplants, respectively. In the single lung transplant arms, the mean %FVC was 76.45 vs. 67.86 for the cold storage vs. EVLP groups, respectively.

At 12 months after transplantation, cold storage double lung transplant and cold storage single lung transplant patients showed higher mean %FEV1 and mean %FVC values compared to EVLP double lung transplant and EVLP single lung transplant patients. In this study, the incidence of BOS was not evaluated; therefore, the differences in FEV1 and FVC values are difficult to interpret for prognostic purposes.

Post-Transplant Bronchoscopy Data

The NOVEL protocol required the following bronchoscopy adverse events to be reported: clinically significant dehiscence, clinically significant stenosis, A2B2 rejection, and infection treated with a systemic antibiotic. Table 24, below, provides a summary of the results:

Table 24 - Bronchoscopy Data

	EVLP	Control
TOTAL # Patients per Arm	31	31
TOTAL # Patients with Incidence	16	13
Total Number of Bronchoscopies:	71	76
Total Number of Bronchoscopies with AEs*	29	25

Bronchial AEs								
	EVLP				Control			
	# of Patients*	# of Incidence	Number of Device Related Incidences	Serious EVLP	# of Patients*	# of Incidence	Number of Device Related Incidences	Serious Control
Total # of Infections:	9	14	0	0	6	11	0	1
Total # of A2 or B2 Rejections:	4	6	0	1	3	3	0	1
Total # of Stenosis:	2	4	0	3	1	3	0	3
Total # of Dehiscences:	0	0	N/A	N/A	1	1	0	0
Total # of Other:	8	9	0	1	6	10	0	2

A2 = mild acute rejection

B2 = high grade airway inflammation (bronchioles only)

The EVLP and control groups did not experience any anastomotic dehiscence. Four (4) EVLP subjects experienced stenosis, three (3) of whom recovered. An EVLP subject who died seven (7) months after transplant sustained an aortic injury prior to the lung transplant, leading to a cascade of events, including sepsis, pneumonia, PGD Grade 3, acute rejection, bronchial stenosis, and skin infections. The control group had two (2) subjects with stenosis, one (1) who recovered and the other who died five (5) months post-transplant.

The incidence of bronchial complication (e.g., dehiscence or bronchial stenosis) was comparable across groups.

Thoracic and Infectious Adverse Events

Adverse events were collected for the first 12 months post-transplant and the severity and causality was assigned by the site investigation or co-investigator. A summary of all adverse events follows in Table 25 below. The infections and infestations include skin infections, nosocomial infections, upper respiratory viral infections, and ear, nose and throat infections. All pneumonia (viral and/or bacterial) were reported under the respiratory, thoracic and mediastinal disorders.

Table 25 - Adverse Events /Infections by Preservation Method (12-month analysis)

	EVLP (n=31 patients)	Control (n=31 patients)
AE System Organ Class	# of Patients with Event	# of Patients with Event
Non-Resp Infections and infestations	5 (16%)	3 (10%)
Fungal infection	0	1 (3%)
Viral infection	1 (3%)	0
Bacterial infection	4 (13%)	2 (6%)
Infection, other	0	0
Respiratory, thoracic and Mediastinal disorders	22 (71%)*	16 (52%)*
Pneumonia	6 (19%)	8 (26%)
Pneumothorax/ Hemothorax/ Hydropneumothorax	11(35%)	3 (10%)
Dyspnea/Respiratory Distress	8 (26%)	3 (10%)
Pleural effusion/ Pseudomembrane	6 (19%)	5 (16%)
Chest pain	1 (3%)	0
Viral/URI/Fungal	5(16%)	2(6%)
Other	4 (13%)	2(6%)

* Twenty-two EVLP patients and 16 controls experienced at least one event categorized as “respiratory, thoracic and mediastinal disorders,” and some experienced multiple events. There were a total of 41 incidences of “respiratory, thoracic and mediastinal” disorders in EVLP patients and 23 incidences in control patients.

All of the reported adverse events are consistent with adverse events usually observed after lung transplantation.

Fungal, viral, and bacterial infections were numerically higher in the EVLP group: 19% compared to 6% in the control group. Similarly, the incidence of respiratory and thoracic disorders was higher in the EVLP group (61%), compared to the control group (35%). The incidence of pneumonias was similar across groups.

Allograft Rejection

Table 26 below provides a summary of the transbronchial biopsy results.

Table 26 - Rejection Biopsy Results

Rejection Biopsy Results		
	EVLP	Control
Total # Subjects Reviewed	31	31
Total # Subjects With TBB	29	30
Total Number of TBB Completed	154	157
Total # Bronchs without TBB	17	14
Total # Biopsy Resulting in A0	112	113
Total # Biopsy Resulting in A1	23	30
Total # Biopsy Resulting in A2	11	9
Total # Biopsy Resulting in AX	7	4
Total # Biopsy Resulting in B0	79	92
Total # Biopsy Resulting in B1	4	4
Total # Biopsy Resulting in B2	2	0
Total # Biopsy Resulting in BX	52	40
Total # Biopsy Resulting in R	3	3
Number of Patients with A2 or B2 Rejection	10	5
Number Patients with A2 or B2 Rejection Resolved	8	3
Number of Patients with A2 or B2 Rejection Ongoing	2 (A2B1R now A0B1R) (A2 now A1)	2 (A2 now A1) (A2B0 now A2B0)

Abbreviation	Definition
TBB	Transbronchial Biopsy
A	Acute Rejection
A0	None
A1	Minimal
A2	Mild
A3	Moderate
A4	Severe
X	Ungradeable (not enough tissue)
B	Airway Inflammation (Bronchioles Only)
B0	None
B1 or B1R	Low Grade
B2 or B2R	High Grade
X	Ungradeable (not enough tissue)

Each study group had one (1) patient with two (2) biopsies yielding A2B2 rejections as ongoing.

The number of patients with trans-bronchial biopsies (TBB), and the number of TBBs performed in these patients was comparable across groups. The number of patients with rejection grades A2 or B2 was 10 and 5 in the EVLP and cold storage arms, respectively.

The numerical difference in the incidence of acute rejection episodes grade A2 or B2 is considered comparable across study arms.

Summary of the NOVEL Trial Results

Table 27 below summarizes the NOVEL trial results.

Table 27 - NOVEL Trial Outcomes

	EVLP-Tx (n=31)	Cold Storage (n=31)
PGD Grade 3 at 72 hours	10%	3%
Thirty-day survival	97%	100%
One-year survival	84%	93%
FEV1% and FVC% 6 and 12 months after transplantation	Lower mean values than control	Higher mean values than EVLP
Infections and infestations	19%	6%
Pneumonias	13%	10%

The NOVEL study was not powered to show statistical differences in outcomes. Thirty-day survival was comparable across groups. One-year survival was 84% and 93% in the EVLP and CS arms, respectively.

The incidence of PGD Grade 3 at 72 hours was three times (3) higher in the EVLP group, compared to the CS control group. Patients that required ECMO support were automatically scored as PGD Grade 3 independent of their graft status, and in two cases, EVLP patients were given Grade 3 due to being on ECMO prior to the transplant procedure (one due to inability to oxygenate on one-lung ventilation and the other for an aortic dissection). These two (2) EVLP patients may not have truly been Grade 3; however, it is unclear given the available data.

PFT data showed numerically better %FEV1 and FVC in the CS group compared to the EVLP group. The incidence of BOS was not evaluated. The meaning of the observed numerical differences is difficult to interpret in an underpowered study.

C. Differences between the HELP and the NOVEL Trials

In the HELP trial, the EVLP group was comprised of patients who were transplanted with high risk (i.e., non-ideal, donor lungs). High risk donor lungs were defined based on clinical criteria, and underwent EVLP accordingly. These lungs were not offered to other transplant programs. In contrast, in the NOVEL trial, non-ideal donor lungs were simultaneously offered to other transplant centers, thus defining an increase in donor lung utilization of non-ideal, not accepted (i.e., “rejected”) donor lungs.

According to the ideal donor lung criteria, adequate oxygenation ($\text{PaO}_2 \geq 300$ mm Hg on fractional inspired oxygen of 1.0 and positive end-expiratory pressure 5 cm H_2O) is

required to qualify as a standard criteria donor lung. The Toronto General Hospital experience³ considered the best PaO₂/ FiO₂ ratio of less than 300 mm Hg to allow study entry for high-risk donor lungs. In contrast, the NOVEL trial allowed for a higher PaO₂/FiO₂ ratio of > 300 mm Hg, if multiple blood transfusions, pulmonary edema, or DCD donation were present.

Also, although the perfusion equipment used in the HELP and NOVEL trials were similar and were comprised of the same types of components (e.g., ventilators, pumps, oxygenators), the actual devices used were different. Both trials used STEEN Solution™ Perfusate.

The transplantability criteria were different during the initial and extension phases of the HELP study¹. During the initial phase (e.g., first 22 transplants), it was required that the organs show a delta PaO₂ ≥ 350 mmHg, and stability in PVR, PawP, and lung compliance (defined as < 15 % deterioration during 2, 3 or 4 hours of EVLP). In contrast, for the extension phase (e.g., last 39 transplants, compassionate use), the transplantability criteria changed to an absolute PaO₂ ≥ 400 mmHg, and PVR, PawP, and lung compliance of < 15% deterioration during 2, 3, or 4 hours of EVLP.

For the NOVEL trial, the protocol specified a delta PaO₂ of less than 350 mmHg (measured with an FiO₂ set at 1.0) at two (2) consecutive time periods at 2, 3, or 4 hours of *ex vivo* perfusion and >10% functional deterioration in PVR, compliance, and PawP as criteria for not transplanting a lung after EVLP.

It is unknown if the different PaO₂/FiO₂ cut-offs (≥ 350 and ≥400 mm Hg for the HELP and ≥ 350 mm Hg for the NOVEL) used as transplantability criteria in the HELP and NOVEL trials are equivalent in prognosticating graft performance after transplantation. Table 28 below lists donor lung utilization and incidence in PGD Grade 3 at 72 hours for both studies. The objective for this comparison table is not to determine which study results are “better,” but to emphasize that different populations and differences in protocols may lead to different results.

Table 28 - Donor Utilization and PGD Differences across the HELP and NOVEL Studies

	HELP Trial*	NOVEL Trial
Donor Lung Utilization after EVLP	86%	54%
Donor after Cardiac Death in EVLP groups	44%	7%
PGD 3 @ 72 in EVLP Transplants	2%	10%
PGD 3 @ 72 in Cold Storage Transplants	8.5%	3%

The studies also showed important differences in the incidence of PGD Grade 3 at 72 hours across studies. In the NOVEL trial, the incidence of PGD Grade 3 at 72 hours was higher in the EVLP–transplanted group, compared to the static cold storage controls. While in the HELP trial, the incidence of PGD Grade 3 at 72 hours was higher in the static cold storage controls, compared to the EVLP group.

The HELP trial showed higher proportions in donor lung utilization. It is worth emphasizing that any increase in lung utilization rate is a benefit. The proportion of DCD donors was higher in the HELP study.

D. Overall Conclusions from the HELP and NOVEL Studies

The study’s primary endpoints for the HELP and NOVEL studies were the incidence of primary graft dysfunction Grades 2 and 3 at 72 hours after transplantation, and 30-day mortality, respectively.

The studies were not powered to demonstrate statistical differences across study groups for the studied endpoints, and given the differences between the NOVEL and HELP trials, the interpretation of the study results should be evaluated separately. Pooling data from the two (2) studies may be challenging to interpret; therefore, the overall conclusions emphasize the clinical perspective as to whether the outcomes were acceptable.

Outcomes

- Primary and secondary endpoints for the EVLP group and the control group were comparable; however, The HELP and NOVEL studies were not powered to demonstrate statistical differences across study groups for the studied endpoints.
- In general, the short term outcomes of the EVLP patients were comparable to conventional cold storage transplants. In the NOVEL study, 30-day survival was 97% vs.100% in the EVLP and control arms, respectively. One-year survival was comparable across EVLP (87%) and control groups (93%).

- Data from the HELP study showed comparable survival at three (3) years (i.e., 67.9% in the EVLP group *versus* 71.2% in the cold storage group). A solid conclusion on long term graft survival is limited because only 28 out of 61 EVLP patients were included in the 3-year survival analyses (see Table 8). Long-term outcomes (e.g., graft survival and function (incidence of BOS)) should be addressed in a post-approval study (PAS).
- The incidence of PGD Grade 3 at 72 hours showed numerical differences between the EVLP and cold storage groups (see Table 28); however, the results are considered comparable across groups in both trials.
- The rate of rejection episodes was comparable between the two treatment groups in both studies.

Specifically for the NOVEL trial:

- There were imbalances across groups: more CVA/stroke donors enrolled in the control group; and more IPF recipients enrolled in the EVLP group (this difference was significant). However, Kaplan-Meier Survival analyses adjusted for IPF recipients-only did not find any increase in mortality in the EVLP group.
- The LAS at transplant included 90% and 81% in the lower priority strata, denoting comparable and predominantly lower risk cohorts.
- In general, most of the donor and recipient characteristics were similar across EVLP and control groups; therefore, similar short- and long-term outcomes should be expected across study arms.
- The secondary endpoints of ECMO, mechanical ventilation, PGD at 24 and 72 hours, ICU/ hospital lengths of stay, and one-year survival demonstrated clinically comparable outcomes between the study groups.
- The incidence of infections and thoracic complications were numerically higher in the EVLP group. These differences are considered clinically comparable.
- Both the EVLP and cold storage donor lungs demonstrated satisfactory lung function early after transplantation. We conclude that four-hour normothermic EVLP-transplanted lungs provided comparable early lung function after transplantation to the standard cold storage method.
- Double and single lung transplants in the CS control group showed higher FEV1% values at 12 months after transplantation, compared to the double and

single EVLP lung transplant groups, respectively. However, the observed numerical differences are difficult to interpret in the absence of BOS data.

Donor lung utilization

- UNOS reports on the donor lung match runs from the NOVEL study indicate that the XPS™ with STEEN Solution™ Perfusate increased the utilization rate of initially unacceptable (i.e., “rejected”) donor lungs. The lung utilization rate after EVLP was 54% for all categories of initially unacceptable donor lungs.
- The main reasons for donor lung non-acceptance were lung edema and pre-retrieval PaO₂/FiO₂ < 300 mm Hg. These donor lungs were subsequently transplanted after EVLP in 62% and 33% of cases, respectively.

Ex-vivo lung function during EVLP

Ex-vivo lung function during EVLP was used in both trials as criteria to determine donor lung transplantability. These criteria showed differences across studies and study periods; therefore, we cannot merge all data for analyses. The conclusions from the NOVEL data are presented below.

- Low delta PaO₂ was the most common reason to reject lungs for transplantation after EVLP.
- The delta PaO₂ criterion for transplantability was met in 55% of the donor lungs transplanted after EVLP, and 28% of the donor lungs that were not transplanted despite meeting the delta PaO₂ criteria (see Table 18).
- Stability (i.e., ≤10% deterioration) in the lung function parameters during EVLP was met in 60%, 80%, and 80% of the non-transplanted lungs after EVLP, for PVR, lung compliance, and PawP, respectively (see Table 18).

All these data indicate that some lungs were transplanted post-EVLP, even when they did not meet the pre-specified criteria. Similarly some donor lungs were not transplanted despite having met the transplantability criteria. All these cases represent protocol deviations in which the decisions for transplantation were made by the transplanting surgeon regardless of the pre-specified EVLP lung function transplantability criteria.

FDA was unable to clarify the relative contribution of the pre-specified transplantability criteria in determining which donor lungs should be transplanted after EVLP (i.e., which donor lungs will perform well after transplantation). Furthermore, it is not clear whether the lung function data provided by the XPS™ System is comparable to data obtained from a donor pre-explant for transplant suitability determination purposes. 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 during EVLP in defining transplantability requires additional understanding and validation.

XI. 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 six (6) investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. RISK PROBABLE BENEFIT ANALYSIS

A. Safety Threshold and Probable Benefit for HDE approval

HDE approval based on the demonstration of safety and probable benefit; however, in lung preservation, lack of efficacy compromises safety. As a result, the safety of the device must be weighed against a certain degree of efficacy and the potential clinical benefits of the device.

B. Probable Benefits

- The XPS™ System with STEEN Solution™ Perfusate demonstrated the benefit of increasing the donor lung utilization rate by rescuing initially unacceptable (i.e., “rejected”) donor lungs.
- The XPS™ System with STEEN Solution™ Perfusate extended donor lung preservation time without significantly compromising short-term outcomes.
- Lung functional assessments during EVLP showed a prognostic potential to identify lungs that will “perform well” after transplantation.
- The benefit of decreasing lung allograft candidates’ mortality while on the waiting list was not demonstrated. FDA does not expect a significant decrease in waiting list mortality when EVLP lungs are transplanted into patients with low priority LAS recipients, as occurred in the NOVEL trial.
- The post-transplant survival benefit of the EVLP lung transplant recipients was not analyzed.

C. Safety of Transplanting Initially Non-Acceptable Lungs after Normothermic EVLP

- The safety database was small, as expected for an HDE application.
- Based on the data provided, the Agency concluded that the short-term safety of the XPS™ System with STEEN Solution™ Perfusate device has been demonstrated.
- Data available did not allow for a statistical evaluation of preservation methods and particular adverse events.
- The incidence of PGD Grade 3 at 72 hours showed numerical differences between the EVLP and cold storage arms (see Table 28). These results are considered comparable across groups in both trials.
- Thirty-day data and available data on one-year survival rates showed comparable results across study groups.
- Long-term outcomes (e.g., beyond one year) were not available from the NOVEL trial. Three-year survival data from the HELP study showed comparable survival at three (3) years, 67.9% in the EVLP group *versus* 71.2% in the cold storage group. A solid conclusion on long term graft survival is limited because only 28 out of 61 EVLP patients were included in the 3-year survival analyses (see Table 8). FDA concludes that long term outcomes (e.g., graft survival and function (incidence of BOS)), should be addressed in the PAS study.
- One (1) year PFT data showed numerically better %FEV1 and %FVC in the CS control groups compared to the EVLP groups. BOS complications were not collected and analyzed as part of the NOVEL study design; therefore, FDA was unable to determine if lungs perfused with the XPS™ System with STEEN Solution™ provide comparable one-year BOS complications and comparable long-term lung allograft survival to standard cold storage lung transplants.

D. Safety of *Ex-vivo* Lung Function Assessment during EVLP to Determine Transplantability

- The value and relative contribution of the EVLP functional assessments (i.e., transplantability criteria) in determining lung transplantability has not been established, although they should remain part of the EVLP treatment and device.

The utility of the EVLP transplantability criteria to prognosticate immediate allograft function (i.e., absence of PGD) after transplantation is unknown.

- *Ex-vivo* lung function parameters during EVLP to reassess lung function and determine transplantability require further refinement and validation to determine how they compare to similar parameters obtained from donors.
- The Advisory Panel recommended that these parameters be evaluated in future studies.

E. Risk Probable Benefit Analysis Conclusion

In summary, based on the analyses of the available data from the HELP and NOVEL trials, we conclude that the XPS™ with STEEN Solution™ Perfusate has demonstrated short term safety comparable to the standard cold storage method and has demonstrated the probable benefit of increasing the lung donor pool. Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury. This takes into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XIII. PANEL RECOMMENDATION

At an advisory meeting held on March 20, 2014, the Gastroenterology Devices Advisory Panel voted 10-0-0 (yes, no, abstain) that there is reasonable assurance the device is safe, 10-0-0 that there is reasonable assurance that the device demonstrates probable benefit, and 10-0-0 that the probable benefits of the device do outweigh the probable risks in patients who meet the criteria specified in the proposed indication.

The panel meeting summary can be found at:

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Gastroenterology-UrologyDevicesPanel/UCM390525.pdf>

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the XPS™ with STEEN Solution™ Perfusate will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device outweighs the risks of illness or injury, and issued an approval order on August 12, 2014.

The final conditions of approval cited in the approval order are described below.

Long-Term Evaluation Study for XPS™ System with STEEN Solution™ Perfusate

The purpose of the study is to evaluate the longer-term safety of the XPS™ System with STEEN Solution™ Perfusate, and to collect quality of life data for patients who were

transplanted with an EVLP treated lung. This will be a prospective, multicenter, two-arm study with a total of 252 patients, consisting of both a premarket cohort and newly enrolled patients. The treatment arm will consist of 126 patients who receive EVLP-treated lungs that were initially considered unacceptable, and the comparator arm will consist of 126 patients who are transplanted with standard lungs that were preserved with cold storage method. The study will enroll patients in six to 20 clinical centers in the United States. The study participants will be followed for three years after transplantation. Data at two and three year time points will be collected through the United Network of Organ Sharing (UNOS) Registry. The primary endpoint is the non-inferiority of the three-year survival rate of the EVLP group, as compared to the comparator group. The secondary endpoints will include quality of life (i.e., functional status, physical capability, and employment status), episodes of rejection, as described by the UNOS registry, and lung function measured by Forced Expiratory Volume (FEV1) two and three years post-transplantation. Other safety outcomes to be collected will include bronchiolitis obliterans syndrome, hospitalization for rejection or infection, bronchial strictures, graft failure and death at two and three years post-transplantation. Additionally, EVLP transplant suitability will be analyzed by summarizing (with confidence intervals) the data collected on lungs undergoing the EVLP procedure by viable/not viable for transplant.

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

XV. APPROVAL SPECIFICATIONS

Directions for Use: See the Professional Labeling.

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

Postapproval Requirements and Restrictions: See approval order

XVI. REFERENCES

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