

XVIVO Perfusion System (XPS™) with STEEN Solution™ Professional Labeling



Ref: 19030 (US) and 19040 (CE)
Serial Numbers: XPS0101+

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Subject to Technical Changes

Due to continuous product improvements, the illustrations and technical information found in the XPS User's Guide may differ (slightly) from the current version of the device.

User Guide References

This document was created using information from:

- CardioHelp User's Manual/English/0.9.0
- CardioHelp XVIVO/Technical Data/Maintenance/ English/100813
- Flow/bubble sensor/ Technical Data/English/100812
- Hamilton C2 Operator's Manual 624131/02 Software version 1.1.x (April 2009)
- Hico-Variotherm 550 Instructions for Use/ REF 542801 Rev.2-08/05

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XVIVO Perfusion System (XPS™) with STEEN Solution™

Professional Labeling

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READ ENTIRE CONTENTS PRIOR TO USING THIS PRODUCT

1. PRODUCT INDICATION FOR USE

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.

1.1. User Qualifications

This product is intended for use only by qualified medical professionals trained in the particular technique and/or surgical procedure to be performed.

1.2. Rx ONLY - PRESCRIPTION USE ONLY

Caution: Federal law restricts this device to sale by or on the order of a physician.

2. CONTRADICTIONS

There are no known contraindications.

3. WARNINGS

3.1. General Warnings

The safety and effectiveness of the XPS™ System with STEEN Solution™ Perfusate device were not evaluated with ideal criteria donor lungs.

3.2. Risk for Contamination and Mechanical Trauma

The degree of organ manipulation required for airway and vascular cannulation carries the potential for contamination and mechanical trauma of the donor lungs. Even though not contraindicated, it is not recommended to use an organ with evident signs of mechanical trauma or major contamination.

3.3. XPS™ Machine Operation-Related Warnings

See Warnings and Precautions in the XPS™ System Instructions for Use manual.

3.4. STEEN Solution™ Warnings

The responsibility to adhere to the approved labeling and Instructions for Use rests with the user. The Instructions for Use are only provided as suggestions for procedure. The user must, on the

basis of his or her medical training and experience, evaluate the suitability of this procedure. When administered systemically, human serum albumin and Dextran have been associated with rare allergic reactions. However, no such reactions have been reported with either of these substances when used for *ex vivo* lung preservation.

4. PRECAUTIONS

4.1.XVIVO Lung Cannula Set™ Precautions

Store at room temperature. Use only undamaged/ unopened containers. Single Use Only.

4.2.XVIVO Organ Chamber™ Precautions

Store at room temperature. Use only undamaged/ unopened containers. Single Use Only.

4.3.XVIVO Disposable Lung Circuit™ Precautions

Store at room temperature. Use only undamaged/ unopened containers. Single Use Only.

4.4.XVIVO Disposable Lung Kit™ Precautions

Store at room temperature. Use only undamaged/ unopened containers. Single Use Only.

4.5.XPS™ Machine Operation-Related Precautions

See Warnings and Precautions in the XPS™ System Instructions for Use manual.

4.6.STEEN Solution™ Precautions

STEEN Solution™ is intended for single use only and MAY NOT BE REUSED. Any leftover solution must be disposed of after the procedure.

4.7.Do not use STEEN Solution™ if the solution is not clear, the bottle is damaged, the flip-tear seal has been tampered with, or if the “use by” date has expired. Transplant Suitability Post-Ex Vivo Lung Perfusion (EVLP)

The responsibility for correct clinical use and interpretation of the lung function evaluations during EVLP in determining transplant suitability resides exclusively with the transplant surgeon.

Like in any other clinical decision, all available data should be taken into consideration when determining the suitability of an organ for transplantation; that is, the transplant surgeon is clinically satisfied with the lung evaluation. This criterion should take priority, since the transplant surgeon is the ultimate responsible person for safely transplanting EVLP lungs. The use of the EVLP lung physiologic evaluations in determining transplantability (e.g., EVLP transplantability criteria) has been evaluated in the clinical studies, including the NOVEL trial (see summary of NOVEL study below). Validation has not occurred as to whether the parameters are adequate as surrogates for *in vivo* performance.

The use of ex-vivo perfusion/ventilation discrete parameters on their own to determine transplant suitability according to the two sets of transplantability criteria used in the NOVEL and NOVEL EXTENSION respectively have not been validated. Clinicians should exercise discretion when using these criteria as the main decision-making tool for transplantability and instead utilize the perfusion/ventilation trends coupled with EVLP x-rays and bronchoscopies and their clinical expertise to make decisions on transplant suitability. Two different transplant suitability criteria (NOVEL: 2 consecutive delta PaO₂s ≥ 350 vs NOVEL Extension: 2 non-consecutive delta PaO₂s ≥ 350 OR 1 absolute PaO₂ > 400) have been used in the NOVEL and NOVEL EXTENSION respectively, and neither of these criteria have been validated. The transplant suitability criteria between the NOVEL and NOVEL Extension studies have shown no difference in survival and/or incidence of

Primary Graft Dysfunction (PGD).

5. DESCRIPTION

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, extracellular (low potassium) electrolyte solution containing human serum albumin (HSA) and dextran 40. The solution has a colloid-osmotic pressure (COP) so that during perfusion a physiological pressure and flow can be maintained in the lung without the development of pulmonary edema (fluid accumulation in the air spaces and parenchyma of the lungs).

The XPS™ System is an integrated cardiac bypass system comprised of various components, such as a centrifugal pump for perfusion of the preservation solution, a heater/cooler unit, a ventilator, perfusate gas monitors, and display monitors.

The XPS™ System is responsible for housing the organ for preservation, providing the normothermic environment, and perfusing the organ with the STEEN Solution™. Please see the XPS™ Instructions for Use manual for a more detailed device description and system set-up and operation information, including flow and perfusion rates, ventilation rates, duration of flushing, and other operational parameters.

5.1. STEEN Solution™ Description

The STEEN Solution™ is supplied sterile in a bottle made of PETg and equipped with a PE screw cap lined with a silicone septum closure, which facilitates aseptic transfer of the solution. The screw cap is sealed by a tamper evident plastic sleeve. The STEEN Solution™ product insert should be read prior to use of this product.

5.2. XPS™ Machine Description

The XPS™ System is an integrated cardiac bypass system comprised of various components, such as a Maquet CardioHelp centrifugal pump (K102726), the HicoVariotherm Heater/Cooler, the Hamilton C2 ICU (intensive care unit) pressure-controlled ventilator (K092148), the perfusate gas monitors, and the display monitors.

5.3. XVIVO Lung Cannula Set™ Description

The XVIVO Lung Cannula Set™ is a sterile, single-use set intended to be used to connect isolated donor lungs to an extracorporeal perfusion system for ex-vivo assessment

5.4. XVIVO Organ Chamber™ Description

The XVIVO Organ Chamber™ is a sterile, single-use container intended to be used as a temporary receptacle for isolated donor lungs in preparation for eventual transplantation into a recipient.

5.5. XVIVO Disposable Lung Circuit™ Description

The XVIVO Disposable Lung Circuit™ is a single-use, disposable extracorporeal perfusion circuit intended to be used with the XVIVO Perfusion System (XPS™) to facilitate perfusion of STEEN Solution™ through isolated donor lungs in preparation for transplantation into a recipient.

5.6. XVIVO Disposable Lung Kit™ Description

The XVIVO Disposable Lung Kit™ contains a number of single-use, disposable sterile and non-sterile items intended to be used with the XVIVO Perfusion System (XPS™) for *ex vivo* evaluation of donor lungs.

The XVIVO Disposable Lung Kit™ contains the following items: Fluid Level Sensor, Pressure Sensor Line, sterile XVIVO Lung Cannula Set™, Linb-o Breathing Circuit, Ventilator Flow Sensor, sterile bacterial/viral filter, and sterile drape. The Fluid Level Sensor, Pressure Sensor Line, and Limb-o Breathing Circuit are not organ contacting.

6. OPERATIONS

Refer to the XPS™ Instructions for Use manual and product inserts for the operation and performance of each component of the XVIVO Perfusion System.

6.1. Normothermic Ex Vivo Lung Perfusion (EVLP)

Normothermic EVLP may permit utilization of initially unacceptable excised donor lungs which are currently often discarded despite the relatively reversible nature of their imperfections. The ultimate objective of the EVLP procedure is to expand the donor organ pool and thus possibly reduce mortality and morbidity on the transplant list.

EVLP with STEEN Solution™ will help increase the pool of available organs by allowing assessment of marginal lungs in optimized conditions. Several mechanisms have been proposed to contribute to this:

- The warming and reperfusion period allows time for lung preservation in an optimized environment. The ex vivo perfusion is carefully controlled using a lung-protective strategy (see XPS™ Instructions for Use manual).
- The physiologic problems caused by neurogenic pulmonary edema in the organ donor with respect to electrolytic balance, colloid-osmotic pressure, and temperature may be restored during the protective reperfusion period.
- Any remaining donor blood still in the lungs (containing coagulation factors, complement, activated white cells, inflammatory cytokines, and non-physiological substances, including drugs used during donor management) is diluted or filtered away during EVLP. This washing out benefit is not achieved with current hypothermic perfusion as the cold temperature induces vascular constriction within the lung, preventing complete flushing.
- It may facilitate removal of clots in the pulmonary circulation through the use of transient retrograde perfusion at the beginning of the procedure.
- The ex vivo system provides an environment for recruitment and re-expansion of atelectatic lung areas because it allows for all ventilatory volumes and pressures to be transferred directly to the lungs without interference of the chest wall and diaphragm.
- It allows time to assess and clean/suction bronchial secretions.
- The dextran in the perfusate solution facilitates perfusion of the pulmonary micro-vasculature.

6.2. EVLP Step by Step Overview

1. Identify if lung meets non-acceptance criteria and EVLP criteria, perform pre-EVLP assessments.
2. If yes, retrieve lung per standard lung protocol.
3. Perform the EVLP procedure in accordance with the XPS™ Instructions for Use manual.
4. Evaluate lung for transplant suitability
5. Transplant or discard lung in accordance with the center policy.

See the XPS™ System Instructions for Use manual for more detailed device description and system

set-up and operation information, including flow and perfusion rates, ventilation rates, duration of flushing, and other operational parameters.

7. PATIENT EDUCATION

It is important to adequately inform patients who might be receiving initially unacceptable, reassessed lungs treated with EVLP about the risks to health and probable benefits. Patient education is critical so that they may be able to make informed decisions, and should be performed when a patient is added to the organ transplant waiting list. Organ quality, EVLP treatment and reassessment of initially unacceptable lungs should be discussed with patients when they are awaiting an organ as an option for their eventual transplantation.

8. CLINICAL SUMMARY

Data from the HELP and NOVEL clinical trials were 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 (see Table 1, below). The NOVEL and NOVEL Extension Study were used to support the Safety and Efficacy of EVLP with the XPS™ and STEEN Solution™. The NOVEL Extension trial, as depicted in Table 1, includes the NOVEL study cohort that was considered in the HDE.

Table 1: Supporting Clinical Studies

Clinical Trial	EVLP Transplanted	Cold Storage (Control)
HELP Trial (Canadian Trial)¹ Normothermic EVLP for an Improved Assessment of Donor Lungs for Transplantation (2008-2010)	N = 50	N = 253
NOVEL Trial (U.S. Trial)² Normothermic EVLP as an Assessment of Extended/Marginal Donor Lungs (2011-2013)	N = 31	N = 31
NOVEL Trial Extension Trial (U.S. Trial)³ Normothermic EVLP as an Assessment of Extended/Marginal Donor Lungs (2011-2018)	N = 110	N = 116
¹ Cypel M., et al., Experience with the first 50 ex vivo lung perfusions in clinical transplantation. J Thorac Cardiovasc Surg, 2012 Nov. 144(5): p. 1200-6 ² Cohort submitted in HDE application. ³ Cohort submitted in PMA application,		

The NOVEL Extension Trial was an extension of the NOVEL Study and continued to accrue patients into the study with a change of primary outcomes from 30 day survival to PGD 3 at 72 hours and Survival at one year post transplant.

The NOVEL and NOVEL Extension study data showed that the pre-specified 12% non-inferiority margin between marginal lungs treated by the XPS™ System with STEEN Solution to standard criteria lungs preserved by the conventional, cold storage method was not met for the co-primary endpoint when all-cause mortality was considered in the survival analysis, and all subjects using ECMO prior to transplant were included in the PGD 3 analysis (the all cause-mortality survival rates were 94% and 86% for the control and EVLP arms, respectively).

The NOVEL and NOVEL Extension trial meets the primary endpoints using the Lifetime Survival Analysis (Specific Cause Mortality), defined as All-Cause Mortality with adjudicated Confounding Risk Factors Mortality excluded from the analyses, and exclusion of PGD 3 at 72 hours if ECMO was

initiated prophylactically (pre-lung implant). The Safety Committee was responsible for the adjudication of all Major Lung Events, Deaths, and Lifetime Survival Analysis (Specific Cause Mortality) 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.

For the 72-hour PGD Grade 3 co-primary endpoint, the independently adjudicated PGD 3 rates were 16% and 9% in the control and EVLP groups, respectively (including all subjects regardless of extracorporeal membrane oxygenation (ECMO) use), meaning that the pre-specified 12% non-inferiority margin was not met.

In addition, a post-hoc comparison to the United Network for Organ Sharing (UNOS) Scientific Registry of Transplant Recipients (SRTR) 12-month survival data from the same study centers as those of the NOVEL and NOVEL Extension showed comparable survival (86% and 88% for the EVLP and UNOS control, respectively). An additional post-hoc analysis on the UNOS dataset was performed on the next available “control,” or the next available transplanted patient who met study inclusion/exclusion criteria. The 1-year survival for that cohort was 89% which was similar to the EVLP arm (86%).

Similarly, a post-hoc analysis of the PGD co-primary endpoint was performed, comparing the EVLP data to the data from the National Institutes of Health (NIH) Lung Transplant Outcomes Group (LTOG) dataset (Diamond, et al., 2013), demonstrating comparable incidence of PGD at 72 hours (16% for the EVLP arm vs. 16.8% for the LTOG dataset).

8.1. Study Objectives

The goal of the NOVEL/NOVEL Extension trial was to demonstrate the safe and effective use of the XVIVO Perfusion System™ (XPS™) with STEEN Solution™ to increase the availability of transplantable donor lungs. The XVIVO Perfusion System™ with STEEN Solution™ is indicated for the flushing and temporary continuous normothermic perfusion of initially unacceptable excised donor lungs during which time the function of the ex vivo lungs can be reassessed for transplantation. A total of 216 initially unacceptable donor lungs were evaluated with XPS™, resulting in lungs meeting acceptability for transplant into 110 recipients.

8.2. Study Design

The NOVEL Extension study is a prospective, multi-center, controlled clinical trial intended to evaluate the safety and effectiveness of the XVIVO Perfusion System™ (XPS™) with STEEN Solution™. Donor lungs that are initially considered unacceptable for transplant (not meeting International Society for Heart and Lung Transplantation (ISHLT) transplant criteria) are evaluated for study eligibility using pre-EVLP inclusion/exclusion criteria. Perfusion of these lungs is performed using STEEN Solution™ with the addition of methylprednisolone, heparin and antibiotics. During the EVLP procedure, donor lungs are evaluated every hour to assess organ function. In order to be considered eligible for transplant, EVLP-treated lungs are evaluated using post-EVLP inclusion/exclusion criteria.

Lungs with stable function that meet the post-EVLP eligibility criteria and the surgeon deemed as transplantable are transplanted into a recipient in accordance with the Organ Procurement Transplant Network (OPTN)/UNOS allocation system. All study procedures and data collection following EVLP are done in accordance with site standard of care and UNOS requirements.

8.2.1. Study Design Limitations

Any study design that is open label, limited in sample size, and without randomization and blinding can lead to the introduction of bias. The NOVEL/NOVEL Extension study design had significant unavoidable limitations:

1. Unpredictability of donor lung availability;
2. Inability to randomize to marginal versus conventional;
3. Selective consenting and enrolling of patients with perceived high-risk diagnoses;
4. Small sample size (utilizing previously unacceptable lungs in field of lung transplant).

Due to the above, control subjects were not enrolled into the study per the protocol specifications and the ability to audit this enrollment was limited by HIPAA regulations if study consent was not executed appropriately. To mitigate the aforementioned, an alternative reference was used as a historical control for comparison to the EVLP and NOVEL Control Arms. The historical control reference used as a comparison for PGD at 72 hours was data from the Lung Transplant Outcomes Group (LTOG); the historical control reference used as a comparison for All-Cause Survival was data from the UNOS registry.

Due to the nature of the selection bias in the study control arm, a post-hoc analysis was performed on the UNOS Dataset across the clinical trial centers. This analysis makes use of data from the UNOS registry. UNOS is a private, non-profit organization that manages the national organ transplant system under contract with the federal government. The organization develops standards and policies that affect all transplant centers in the United States. UNOS is required by the Center for Medicare and Medicaid Services (CMS) to collect detailed donor, recipient and outcomes data for all transplants performed at U.S. transplant centers. UNOS transplant data from the 17 centers that participated in the NOVEL Extension study was obtained as part of the NOVEL Extension data analysis and was filtered according to the NOVEL Extension inclusion/exclusion criteria. To permit conformity between the two data sets, an analysis was performed to ensure that the patients in the final UNOS dataset did not differ from the control arm in donor age, sex, cause of death, or median PaO₂ upon acceptance. The recipient population did not differ in terms of age, sex, race, median recipient lung allocation score (LAS) score at time of transplant, and recipient diagnoses for transplant.

The following subjects were excluded from being used as UNOS Controls:

- 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

The UNOS data utilized for this analysis is unbiased as it includes all subjects at NOVEL Extension study sites within the study time frame, and is also a much larger sample size than the control arm. This provides a more accurate assessment of lifetimes of subjects with conventional transplants against which to assess potential risk associated with the use of the EVLP process. An ad-hoc analysis of the UNOS data was performed using the next available “control”, i.e., the next available standard criteria-transplanted patient who met study inclusion/exclusion criteria immediately following the sites’ EVLP transplanted patient. This survival analysis is referenced in Section 10.

The UNOS registry recently (2016) began collecting PGD data and was therefore unable to be used as an effective comparator. The best representation of nationwide incidence of PGD is reported through the Lung Transplant Outcomes Group (LTOG). LTOG is a US National Institutes of Health sponsored, multicenter, prospective cohort study designed to evaluate risk factors for, and rates of, PGD. They performed a 10-center (7 of 10 participated in the NOVEL Extension Study) prospective cohort study. Enrollment was between March 2002 and December 2010 and the primary outcome was ISHLT Grade 3 PGD at 48 or 72 hours post-transplant.

9. SAFETY AND EFFICACY EVALUATION

The effectiveness of this trial is based on the safe, successful transplant of donor lungs that were initially considered unacceptable, thereby increasing the availability of donor organs. Initially unacceptable lungs receive up to 6 hours (as specified in the NOVEL/NOVEL Extension study) of ex vivo lung perfusion (EVLP) using the XVIVO Perfusion System™ (XPS™) with STEEN Solution™. Treated lungs are then re-evaluated for transplantability.

The safety of EVLP transplanted lungs is compared to conventional lung transplant using the co-primary endpoints of 1-year survival and rate of Grade 3 primary graft dysfunction (PGD) at 72 hours post-transplant. Secondary endpoints include PGD score at 24 and 48 hours, ICU and hospital length of stay, post-transplant use of ECMO and mechanical ventilation, pulmonary function tests at 3/6/9/12 months, and quality of life and functional status at 1 year. A comparison of serious Major Lung Events (MLEs) between the EVLP and control study arms is the primary safety endpoint.

9.1.XVIVO Perfusion System™ with STEEN Solution™

The XPS™ system allows for donor lungs that fail to meet transplant criteria to be reconsidered for transplant following up to 6 hours (as specified in the NOVEL/NOVEL Extension study) of ex vivo lung perfusion (EVLP). The use of XPS™ with STEEN Solution™ does not change the process of lung transplantation. Its purpose is to provide the surgeon with additional information and decision-making time prior to transplant.

9.2.Selection of Doses

The composition of STEEN Solution™ has remained the same throughout the study. During EVLP, approximately 3-6 bottles of STEEN Solution™ are placed into the XPS™ system and circulated for one hour while increasing the temperature to normothermia. After the first hour of perfusion, the STEEN Solution™ is replaced with an equal amount. The purpose of this warming and exchange is to dilate the micro-vasculature to cleanse/dilute any residual blood or released inflammatory cytokines from the donor lung.

9.3.EVLP Perfusion Time

Pre-clinical data showed that most lung improvement occurs in the first 4 hours of EVLP. The Toronto HELP study found that significant improvement occurred at 1 hour and continued to improve at 2 hours. At this point, the lung maintained function if it was ultimately transplantable. Based on this testing, the original NOVEL Extension study set a maximum of 6 hours of EVLP.

Overall improvement of lung function is assessed at two time periods, along with a lung x-ray after the first hour and if considering transplantable a second x-ray at any time point. The x-ray provides secondary confirmation of improvement if the reason for initial rejection was pulmonary edema. Edema can 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 ET tube). The minimum duration of EVLP perfusion has been 3 hours in determining transplantability. Lungs that are deemed not transplantable prior to 3 hours do not need a second x-ray.

9.3.1. EVLP Run Time Table

Table 2: EVLP Preservation Time and Cold Ischemic Times					
	Control N=116		EVLP TX N=110		EVLP Not TX N=106
Pre-EVLP Cold Ischemic Time 1					
Median (Range)	NA		208.5	(65-648)	219 (58-723)
Mean (SD)	NA		211.5	90.0	222.1 97.7
EVLP Run Time					
Median (Range)	NA		233.5	(137-405)	202 (34-403)
Mean (SD)	NA		241.0	50.0	206.1 64.8
Post-EVLP Cold Ischemic Time 2					
Median (Range)	NA		278	(56-737)	NA
Mean (SD)	NA		283.0	118.7	NA
Total Cold Ischemic Time					
Median (Range)	314.5	(111-675)	494	(111-904)	NA
Mean (SD)	320.1	106.3	494.4	146.0	NA
Total Out of Body Time					
Median (Range)	314.5	(111-675)	732	(375-1125)	NA
Mean (SD)	320.1	106.3	735.4	157.0	NA

The EVLP run data presented in Table 2 show that most treatments lasted approximately 4 hours. There were limited data for EVLP treatments out to 6 hours (only 2 donor lungs treated for six hours or more and subsequently transplanted); therefore, the recommendations are for a maximum treatment time of 5 hours.

9.4. Treatment

The treatment (EVLP) group are subjects who received transplants of donor lungs treated with ex vivo lung perfusion using the XVIVO Perfusion System™ with STEEN Solution™.

9.5. Ex Vivo Lung Perfusion (EVLP)

Donor lungs experience trauma when death occurs, resulting in the release of inflammatory cytokines and a shift of fluid into the cells limiting adequate gas exchange. Donor lungs meeting the NOVEL study criteria for EVLP are cannulated, perfused with STEEN Solution™, ventilated and warmed to body temperature (normothermia) for a minimum of 3 hours and a maximum of 5 hours. STEEN Solution™ is a hyperosmotic solution that stimulates the movement of fluid out of the cells, thereby improving gas exchange. The EVLP procedure is designed to simulate the lung environment in a living patient using venous input of nitrogen, carbon dioxide and oxygen to mimic the conditions of human respiration.

During EVLP, the physiological parameters of the donor lungs are measured and re-evaluated. EVLP provides the surgeon with additional information and time to assess the lungs in a stable, controlled, normothermic environment.

9.6. Patient Population

The target population includes all patients on the lung transplant wait list who are 18 years of age or older. The NOVEL trial was designed to follow the established and regulated process of organ allocation and wait list prioritization, so patients received lungs based on rules and regulations established by UNOS which is based upon their Lung Allocation Score (LAS) at the time of transplant and region.

9.7. Pre-EVLP Donor Lung Eligibility Criteria

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

- $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg at the time of clinical evaluation, **OR**
- If $\text{PaO}_2/\text{FiO}_2 > 300$ mmHg, 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.

The donor lung is excluded from transplant if any of the following criteria are met:

- 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 criteria can be assessed during or after EVLP but prior to transplant.)

9.8. EVLP Preparation

Once a lung is procured for EVLP, it is flushed with a cold preservative solution (Perfadex), packaged according to industry standards, and transported on ice (cooled to 4-10°C) to the transplant center. After the lung is received by the transplant center it is unpacked, the EVLP cannulas are sutured to the left atrial cuff and pulmonary artery, and it is placed on the XPS™ machine to begin antegrade perfusion (a period of retrograde perfusion occurs prior to antegrade perfusion to remove any clots that might be in the pulmonary artery).

Graft preparation time is measured from the time of unpacking to the start of antegrade perfusion. The lung is warmed and perfused on the EVLP circuit for a minimum of 3 hours and a maximum of 4 hours (6 hours in the NOVEL Extension study) with a 45-minute window in order to be transplanted. Physiological parameters are collected every hour and x-rays are taken at 1 hour and a second time any time after if deemed transplantable. After EVLP, the lung is rapidly re-cooled and placed back on ice in the standard sterile method for organ storage. This time of cold storage after EVLP is necessary to decrease the chance of lung degradation during the implantation procedure.

9.9. Post-EVLP Donor Lung Eligibility Criteria

The following physiological parameters are collected during the EVLP run:

- Flow rate
- Pulmonary artery pressure (PAP)
- Left arterial pressure (LAP)
- Pulmonary vascular resistance
- Peak airway pressure (PawP)
- Mean airway pressure (MawP)
- Peak plateau pressure (pPlat)
- Dynamic compliance (CDyn)
- Static compliance (CStat)
- Tidal volume (VT)
- Positive end expiratory pressure (PEEP)
- Absolute venous oxygen tension (PvO2)
- Absolute arterial oxygen tension (PaO2)
- ΔPO_2 (PvO2-PaO2)

In order to proceed to transplant, the EVLP treated donor lung must meet the following criteria:

- Surgeon must be clinically satisfied with the lung evaluation.
- Stability or improvement in all lung function parameters (PVR, compliance, airway pressure) during perfusion.
- $\Delta PO_2 \geq 350$ mmHg at two time points during EVLP.

If two $\Delta PO_2 \geq 350$ mmHg cannot be obtained, adaptive eligibility criteria may be used. At least three of the four following criteria must be met:

- One $\Delta PO_2 \geq 350$ mmHg or absolute $PO_2 \geq 400$ 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 donor lung is excluded from transplant if any of the following criteria are met:

- All ΔPO_2 s < 350 mmHg (measured with FiO2 set at 1.0) or all absolute PO_2 s 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.

9.10. Recipient Eligibility Criteria

A recipient must meet the following criteria to enroll into the study:

- Requires single or bilateral lung transplant.
- Male or female, 18 years of age or older.
- Subject or subject's representative provides a legally effective 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/1.73m² 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.
 - (CPAP and BIPAP are not exclusionary.)

10. NOVEL/NOVEL EXTENSION STUDY RESULTS

10.1. Summary of Results

10.1.1. Co-Primary Endpoints

The co-primary endpoints are the non-inferiority of EVLP to the control for the 1-year survival rate and the rate of Grade 3 PGD at 72 hours.

An independent three panel safety committee (comprised of two lung transplant surgeons and one lung transplant pulmonologist) perform a quarterly review of a listing of safety data for the EVLP and Control Arm to assess if the events occurring are outside of the expected events in this population. This includes quarterly review and adjudication of all Major Lung Events (MLEs) and Deaths as per the study protocol safety charter. The adjudication reviews causality, cause of death, MLE type, and provides clinical justification for the deaths removed from the specific cause survival analysis. If an event is considered an Unanticipated Adverse Device Effect (UADE), the safety committee and the Independent Safety Monitor (ISM) shall adjudicate and assess unreasonable risk.

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 two blinded independent transplant pulmonologists per the study protocol. The adjudicator's responsibility is 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 is non-consensus between the Investigator and Primary Adjudicator all reports and images will be reviewed and assessed by a secondary adjudicator. The majority PGD score will determine the final score. When one adjudicator provides a score of 3 which is not in consensus with the other adjudicator, a second adjudicator review will take place. If there is a non-consensus decision between the investigator, primary adjudicator, and secondary adjudicator, a second adjudicator review will take place and a consensus will be made between the Primary and Secondary adjudicator.

For both endpoints the non-inferiority margin for the difference in rates is 0.12 and non-inferiority is measured by the appropriate endpoint of a 2-sided 95% confidence interval on the difference in rates.

10.1.2. 1 Year Survival (All Cause Mortality)

Table 3: 1 Year Survival (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
* Subjects transplanted less than 1 year from the cutoff date are not included in the analysis. The UNOS control comparisons are post-hoc and were not specified in the Statistical Analysis Plan.				

The EVLP all-cause mortality 1-year survival rate was 86% versus the Control arm rate of 94%, and these rates were not statistically different at a 0.05 significance threshold (p-value = 0.0718). The 1-year survival rate for EVLP missed the pre-specified non-inferiority endpoint; the 95% CI on the difference in rates (control – EVLP) was (-0.0040, 0.1542) while the confidence interval contains 0, the upper endpoint is above the non-inferiority margin of 0.12. However, the EVLP all-cause 1-year survival rate of 86% was similar to the UNOS Control 1 year survival rate of 88%.

The study had a control arm of convenience, where control subjects were enrolled at convenience rather than matched per EVLP transplant as required by the protocol; this resulted in selection bias in the control arm. This is demonstrated by comparison to the UNOS data; these data include all subjects at NOVEL/NOVEL Extension study sites within the study time frame with study protocol eligibility criteria applied, and thus, provide a population estimate of 1-year survival rates of conventional lung transplants at the study sites. This dataset demonstrated that no site included in the study demonstrated a 1-year survival of greater than 89% for their lung transplant program. This is in alignment with the UNOS/SRTR national averages of 85%, but very different from the Study Control arm 1-year survival rate of 94%.

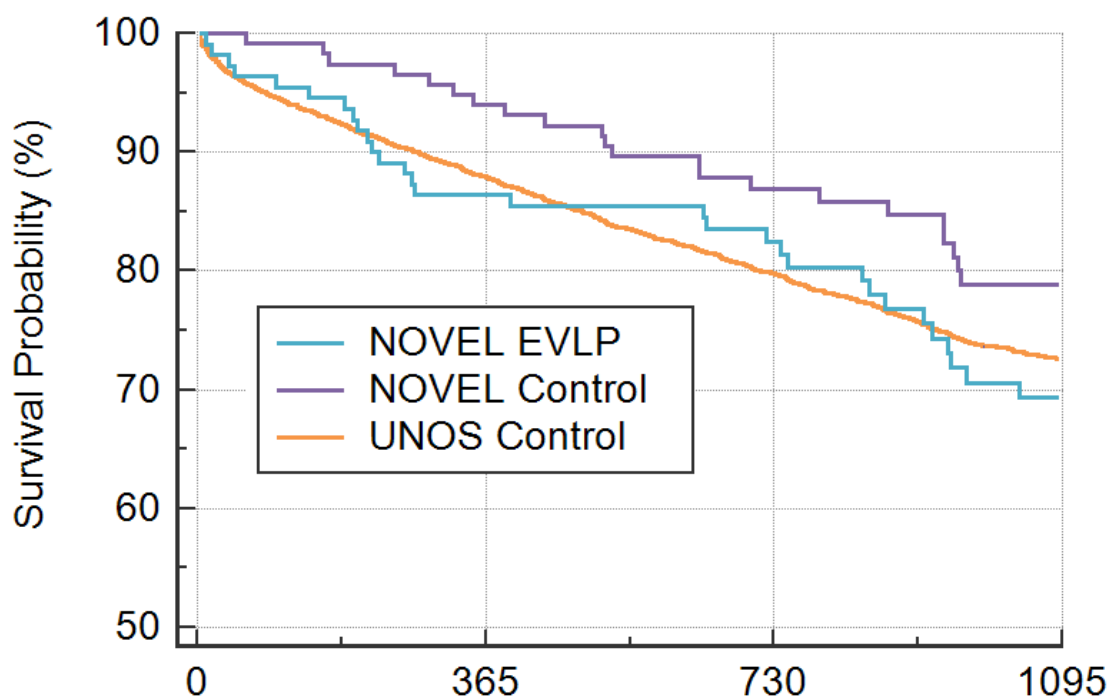
Furthermore, when post-hoc analysis on the UNOS dataset was performed on the next available “control,” or the next available transplanted patient who met study inclusion/exclusion criteria, the 1 year survival for that cohort was 89% as seen in Table 4:

Table 4: Survival at 1 Year - Next Control		
One Year Survival (Overall Mortality)	NOVEL EVLP N = 110	Next Eligible Control N = 93
<i>Survived to 1 Year</i>	95 (86%)	83 (89%)
<i>Expired Before 1 Year</i>	15 (14%)	10 (11%)
<i>Case Not At 1 Year (not included in survival %)</i>	0 of 110 cases 0 living, 0 expired	17 of 110 cases 17 living, 0 expired

The table below shows a comprehensive all-cause mortality death listing for the study:

Table 5: All Cause Mortality Listing					
Subject	EVLP/ Control	Survival Days	Cause of Death	Exclude from Specific Cause Mortality*	Recipient LAS
0123	Control	61	Antibody mediated rejection	No	60.1421
0301	EVLP	10	Reperfusion injury due to cytokine	No	31.6975
0302	Control	250	Renal failure	Yes (All Cause Only)	38.6625
0427	Control	167	Acute or chronic hypercarbic respiratory failure	No	4.4992
0409	EVLP	202	Pulmonary Respiratory failure	No	85.1
0412	EVLP	141	Acute rejection and respiratory failure	No	48.6
0572	EVLP	215	Bacterial septicemia (sepsis)	No	32.4016
0504	Control	159	Airway stenosis and respiratory failure	No	47.0049
0513	EVLP	198	Complications from Aortic Injury	Yes (All Cause Only)	43.224
0522	EVLP	272	Broncholitis obliterans syndrome	No	33.4134
0630	EVLP	19	Liver failure / multi-organ dysfunction syndrome (shock)	No	32.3478
0640	EVLP	262	Unknown/Diagnosed Lymphoma left AMA	Yes (All Cause Only)	32.5632
0609	EVLP	229	Massive hemoptysis secondary to a bronchovascular fistula that occurred following stent placement due to bronchial stenosis.	No	71.9879
0620	EVLP	187	Renal Failure	Yes (All Cause Only)	32.6543
0625	EVLP	275	Native lung cancer (RLL squamous cell carcinoma)	Yes (All Cause Only)	31.734
0703	EVLP	221	Graft versus host disease	Yes (All Cause Only)	34.3122
0809	Control	294	Septic shock caused by aspiration pneumonia	No	33.5
0905	EVLP	47	Sepsis due to colon perforation w/ diverticulitis.	Yes (All Cause Only)	39.6866
1105	Control	349	intracranial hemorrhage	Yes (All Cause Only)	70
1111	EVLP	100	Septic shock	Yes (All Cause Only)	36
1603	EVLP	39	Cardiopulmonary arrest	No	44.6655
1705	Control	324	Respiratory Failure secondary to sepsis	No	35.51

10.1.3. Kaplan-Meier Survival Curve (All Cause Mortality) * from Transplant to 3 Years



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

10.1.4. 1 Year Survival (Specific Cause Mortality)

Table 6: Survival (Specific Cause Mortality)						
	NOVEL EVLP N = 110		NOVEL Control N = 116		UNOS Control N = 4063	
	Deaths	% Survival	Deaths	% Survival	Deaths	% Survival
<i>Specific Cause Mortality*</i>	8	(93%)	5	(96%)	NA	(NA)
<i>Specific Cause Mortality (possibly related to EVLP)</i>	0	(100%)	NA	(NA)	NA	(NA)
* Deaths unrelated to preservation technique or transplant are treated as living for the purpose of calculating specific cause mortality as adjudicated by Safety Committee						

An independent three panel safety committee was used to quarterly adjudicate all MLEs and Deaths. This adjudication reviewed causality, cause of death, MLE type, and provided clinical justification for removal from the specific cause survival analysis. If an event is considered an Unanticipated Adverse Device Effect (UADE), the safety committee and the ISM shall adjudicate and assess unreasonable risk.

Per the statistical analysis plan and as defined by the safety committee, deaths were adjudicated into two categories: all cause and specific cause. This delineation was used to provide a clinical assessment of the risks of the organ preservation and perfusion procedure [EVLP] employed in a high-risk population (patients with end-stage lung disease) using a high-risk procedure (lung transplantation) and management (immunosuppression) with multiple clinical risk factors, in a non-randomized trial with a relatively small sample size. The intent is to remove deaths that have

confounding risk factors that are unrelated to lung preservation or perfusion technique to provide a Specific Cause Mortality to be used in the life time survival analysis.

The confounding risks factors had three categories:

1. Donor/Recent Matching Factors

- e.g. donor selection, size mismatch, recipient co-morbidities.

2. Technical/Operative Decisions

- e.g. intraoperative complications such as aortic injury or delayed chest closure.

3. Known Risks of Transplant (Non-Pulmonary)

- e.g. risks inherent to transplant population such as mental status changes, vascular fragility, immunosuppression use, non-compliance.

There was no statistically significant difference between the EVLP and Control Specific Cause Mortality at 1 year (93% for EVLP, 96% for Control).

The below death listing were adjudicated by the Safety Committee as having confounding risk factors and possibly being unrelated to the EVLP treatment.

Subject	Case Type	Date of TX	Diagnosis Requiring Transplant	PGD @ 72hrs*	Date of Death	Primary Cause of Death
0302	Control	1/20/12	Fibrosis associated with short telomere syndrome	1/1	9/26/12	Renal Failure
0513	EVLP	7/18/12	Fibrosis	3/3	2/1/13	Complications from Aortic Injury
0620	EVLP	6/17/13	Emphysema/COPD/Alpha I Antitrypsin Deficiency	3/3	12/21/13	Renal Failure
0625	EVLP	11/3/13	Emphysema/COPD/Alpha I Antitrypsin Deficiency	2/2	8/5/14	Lung cancer (RLL squamous cell carcinoma)
0640	EVLP	12/20/16	Emphysema/COPD/Alpha I Antitrypsin Deficiency	0/1	9/8/17	Lymphoma
0703	EVLP	7/16/13	Emphysema/COPD/Alpha I Antitrypsin Deficiency	0/1	2/22/14	Graft versus host disease
0905	EVLP	10/12/16	Fibrosis	3/3	11/28/16	Sepsis due to colon perforation w/ diverticulitis
1105	Control	5/13/15	Scleroderma	1/1	4/26/16	Intracranial hemorrhage
1111	EVLP	3/9/17	Emphysema/COPD/Alpha I Antitrypsin Deficiency	3/3	6/17/17	Septic Shock
* Physician's PGD Score (Unadjudicated) / Independently Adjudicated PGD Score						

Table 8: Clinical Justification for Deaths Excluded from Specific Cause Mortality			
Subject	Cause of Death	Clinical Justification	Description of Event
0302 Control	Renal Failure (250 days after transplant)	Donor/ Recipient Matching Factors (co-morbidities)	After uneventful transplant, the subject developed renal failure and was intubated due to hypoventilation caused by fluid overload. 1 week after transplant, subject was found to have gastric and esophageal varices consistent with advanced liver disease and portal hypertension. Subject was found to have a rare congenital malformation of the portal system that masked the signs of liver disease. Varices may have been exacerbated by immunosuppression.
0513 EVLP	Aortic Injury (198 days after transplant)	Technical/ Operative Decisions	No issues with EVLP run. Aortic dissection occurred in OR. Subject was trached due to multi-system failure caused by hypovolemic shock.
0620 EVLP	Renal Failure (187 days after transplant)	Known Risk of Transplant	Unexplained mental status issues, noncompliant with dialysis and BiPAP. Developed renal failure from suprathreshold tacrolimus. Family declined further treatment. The subject's acute kidney injury was thought to be due to aminoglycoside use and suprathreshold tacrolimus levels with an additional component of intravascular volume depletion in the setting of diuresis.
0625 EVLP	Lung Cancer (275 days after transplant)	Donor/ Recipient Matching Factors (co-morbidities)	Smooth EVLP, great post-operative course. Subject developed cancer in native lung, requiring pneumonectomy. Per Safety Committee, cancer likely present at baseline and exacerbated by immunosuppression, may have gone undetected if subject had not received a CAT scan since going on the transplant waiting list.
0640 EVLP	Unknown (262 days after transplant)	Known Risk of Transplant	Originally reported as lymphoma. Subject had lymphoma, but traveled out of state against medical advice. Death occurred at an outside hospital. Since site could not obtain complete records from the outside hospital, they could not definitively establish the cause of death.
0703 EVLP	Graft vs. Host Disease (221 days after transplant)	Donor/ Recipient Matching Factors (co-morbidities)	Subject developed encephalopathy and multi-system failure 6 months after transplant. Diagnosed as graft vs. host disease. Per Safety Committee, the graft vs. host disease so long after transplant is unlikely to be related to EVLP and is a rare immunological response that cannot be detected prior to transplant.
0905 EVLP	Sepsis Due to Colon Perforation (47 days after transplant)	Known Risk of Transplant	Initially reported as respiratory failure. Subject was intubated due to sepsis resulting from colon perforation and died 47 days after transplant. Autopsy found the cause of death was perforated colon due to diverticulitis causing sepsis. Several confounding risk factors: baseline donor lung infection, complicated operative course and risks with immunosuppressants. The donor lung was a CDC high risk that had S. Maltophilia. During transplant the patient could not be weaned off of CPB leading to use of ECMO.

Table 8: Clinical Justification for Deaths Excluded from Specific Cause Mortality			
Subject	Cause of Death	Clinical Justification	Description of Event
1105 Control	Intracranial Hemorrhage (349 days after transplant)	Known Risk of Transplant	Subject presented with left side weakness and was found to have a large intracranial hemorrhage. Subject was made palliative care. Per Safety Committee, vascular fragility due to immunosuppressant medications may have been a factor.
1111 EVLP	Septic Shock (100 days after transplant)	Donor/ Recipient Matching Factors (co-morbidities)	High risk transplant with donor/recipient size mismatch requiring removal of a portion of the donor lung. Subject had a complicated post-operative course involving extended ECMO, tracheostomy, significant stenosis, delayed chest closure, and chest cavity infection. Subject eventually maxed out on ECMO and ventilator and developed sepsis with positive blood cultures and a perforated ulcer. Sepsis likely seeded from ECMO cannula. Per Safety Committee, the event is not caused by EVLP as the mismatch and operative choice are the cause of the sepsis.

10.1.5. Primary Graft Dysfunction @ 72 Hours

Table 9: Primary Graft Dysfunction @ 72 Hours (Independently Adjudicated)					
@ 72 Hours	EVLP N = 110		Control N = 116		p-value (x2)
Grade 0	25	(23%)	37	(32%)	0.1955
Grade 1	51	(46%)	47	(41%)	
Grade 2	16	(15%)	21	(18%)	
Grade 3	18	(16%)	11	(9%)	

Per the protocol the PGD was adjudicated by 2 Independent blinded Lung Transplant Pulmonologists. The adjudication was performed to provide a high quality and objective data point for PGD at 72 hours as this was a co-primary endpoint, and assessment of PGD is partly based upon a clinician's assessment of a chest radiograph which can be subjective. The adjudicator's responsibility is 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 is non-consensus between the Investigator and Primary Adjudicator all reports and images will be reviewed and assessed by a secondary adjudicator. The majority PGD score will determine the final score. When one adjudicator provides a score of 3 which is not in consensus with the other adjudicator, a second adjudicator review will take place. If there is a non-consensus decision between the investigator, primary adjudicator, and secondary adjudicator, a second adjudicator review will take place and a consensus will be made between the Primary and Secondary adjudicator.

Table 10: Primary Graft Dysfunction @ 72 Hours (Non-Adjudicated)			
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%)	
Grade 3	15 (14%)	8 (7%)	0.1233
Below 3	95 (86%)	108 (93%)	

Table 9 shows the adjudicated PGD assessments and Table 9 shows the unadjudicated PGD at 72 hours by the respective site Investigator(s).

The best representation of nationwide incidence of PGD is reported through the Lung Transplant Outcomes Group (LTOG). The published LTOG rate from that study (Diamond, et al., 2013) was 16.8%. That is, 211 of the enrolled 1255 patients across 10 centers developed PGD 3 at 72 hours. Per Christie et al., 2005, the national incidence of PGD is between 10-30%.

PGD at 72 hours was independently adjudicated by a blinded adjudication panel per the protocol, and the incidence of PGD3 at 72 hours in the Study EVLP was 16% (14% unadjudicated rate) which is in alignment with these published expected PGD rates. However, the enrollment of a convenience control arm also impacted the PGD rates in the Study Control group. Using the control arm of convenience as a comparison, the PGD3 measure missed the pre-specified non-inferiority endpoint with the 95%CI on the difference in rates (control – EVLP) being (-0.1563, 0.0204). While the confidence interval contains 0, the lower endpoint is below the non-inferiority margin of -0.12. However, there was not a statistically significant difference at a 0.05 significance threshold (p-value = 0.1633) in incidence of Grade 3 PGD at 72 hours between the EVLP and control arms (16% vs 9%, adjudicated values).

10.2. Secondary Analysis

10.2.1. Pulmonary Function Test (FEV1 % Predicted)

Table 11: 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
Not Done due to Death	4	1	6	3	13	4	15	7
Not Done for another reason (trached/hospitalized/patient noncompliance)	7	8	8	6	8	5	5	4

* 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.

There was no statistically significant difference in FEV1 % predicted at 3, 6, 9, and 12 months.

10.2.2. Primary Graft Dysfunction @ 24 and 48 Hours (Non-Adjudicated)

Table 12: Primary Graft Dysfunction @ 24 and 48 Hours (Non-Adjudicated)			
@ 24 Hours	EVLP N = 110	Control N = 116	p-value (χ^2)
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 (χ^2)
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%)	

There was a statistically significant difference at a 0.05 significance threshold (p-value = 0.0294) in the distribution of PGD rates at 24 hours between the EVLP and Control arms. However, this difference diminishes by 48 hours. PGD3 at 24 hours is not considered a clinically significant indicator of post-transplant outcomes and mortality.

10.2.3. Intensive Care Unit (ICU) and Hospital Length of Stay (LOS)

Table 13: ICU Length of Stay (days)

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

Table 14: Hospital Length of Stay (days)

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

There was no significant difference in ICU or hospital length of stay between recipients of EVLP and control lungs.

10.2.4. Duration of Mechanical Ventilation

Table 15: Duration of Mechanical Ventilation (days)

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

There was no significant difference in days in mechanical ventilation between EVLP and control groups.

10.3. Safety Analysis

10.3.1. Major Lung Events

Table 16: Major Lung Events (Serious and Non-Serious Combined)

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

Table 17: Major Lung Events (Serious Only)

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

Table 18: Major Lung Events (Non-Serious Only)

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

The original NOVEL study used a standard adverse event definition that captured all subject hospitalizations as serious adverse events (SAEs). Due to the high rate of hospitalization among the transplant recipient population, this resulted in the capture of many expected non-pulmonary events. During the transition to the NOVEL Extension study, hospitalization events were captured as either a Major Lung Event, Non-MLE hospitalization, or not reportable.

The following events are captured as Major Lung Events (MLEs) if they meet serious criteria:

- Acute Rejection: Defined as rejection greater than or equal to A2 or B2 (according to the ISHLT grading system) and requiring treatment.

- **Respiratory Failure:** Defined as impairment of respiratory function requiring re-intubation, tracheostomy, or the inability to discontinue invasive ventilator support within 4 days (96 hours) of admission to ICU following transplant surgery due to respiratory issues and not due to sedation issues.
- **Bronchial Complication:** Defined as moderate to severe necrosis (mucosal and/or extending to bronchial wall) at the bronchial anastomotic site due to ischemic injury, with or without bronchial dehiscence (Grade II-IV) verified by bronchoscopy or chest CT, and/or requiring bronchial stent placement, primary repair, pneumonectomy, or re-transplantation.
- **Major Pulmonary-Related Infection:** Defined as a clinical infection of pulmonary origin that is treated with antibacterial/antifungal/antiviral agents (non-prophylactic and not found in the donor lung prior to implantation) Presence of pulmonary infiltrates(s) on chest x-ray along with positive cultures and/or chest CT, and/or positive transbronchial biopsies to confirm infection and rule out rejection should be present unless strong clinical evidence indicates the need for treatment despite negative cultures.
- **Re-Transplant:** Removal of the transplanted lung(s) that was part of the study and implantation of new donor lung(s) in its place due to deterioration of the study lung(s).

Non-MLE hospitalizations for any reason are recorded, but are not considered serious adverse events unless MLE criteria are met. In the original NOVEL trial, the protocol captured non-serious bronchial complications and rejections. The overall incidences of MLEs are similar between EVLP and Control Groups. A review of the MLE results found that the EVLP and Control Groups have similar incidences of rejections, bronchial complications, respiratory failure, major pulmonary infection. Neither study group had any re-transplant.

10.3.2. Non-MLE Hospitalizations

Table 19: Non-MLE Events			
	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.

There was no significant difference between the incidence of non-MLE hospitalization in the EVLP and Control arms at a 0.05 significance threshold.

10.4. Demographics

10.4.1. Donor Demographics

Table 20: Donor Demographics									
Donors	NOVEL EVLP				NOVEL Control		UNOS Control		
	Not Transplanted N = 106		Transplanted N = 110		Transplanted N = 116		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	0.0%	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 21: Donor Demographics

Donors	NOVEL EVLP							
	Not Transplanted N = 106				Transplanted N = 110			
Donor Age	Mean	St. Dev	Median	IQR	Mean	St. Dev	Median	IQR
<i>Years</i>	30.6	11.8	33.5	18.0	34.7	13.2	28.5	22.0
Donor PaO2	Mean	St. Dev	Median	IQR	Mean	St. Dev	Median	IQR
<i>mmHg</i>	352.4	101.9	343.0	136.5	343.8	106.7	363.0	142.8
Donors	NOVEL Control				UNOS Control			
	Transplanted N=116				Transplanted N=4898			
Donor Age	Mean	St. Dev	Median	IQR	Mean	St. Dev	Median	IQR
<i>Years</i>	36.2	13.7	36.0	22.3	35.4	14.3	33.0	24.0
Donor PaO2	Mean	St. Dev	Median	IQR	Mean	St. Dev	Median	IQR
<i>mmHg</i>	413.6	85.6	418.5	96.0	392.9	137.5	423.0	164.0

In general, the mean Donor PaO2 in the NOVEL and UNOS Control cohorts tended to be higher than in the EVLP transplant and non-transplant cohorts.

10.4.2. Recipient Demographics

Table 22: 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						

Table 22: Recipient Demographics						
<i>Bilateral</i>	63	57.3%	81	69.8%	3491	71.3%
<i>Single Left</i>	25	22.7%	21	18.1%	772	15.8%
<i>Single Right</i>	22	20.0%	14	12.1%	635	13.0%
Single/Double						
<i>Double</i>	63	57.3%	81	69.8%	3491	71.3%
<i>Single</i>	47	42.7%	35	30.2%	1407	28.7%

Table 23: Recipient Demographics						
EVLP Recipients		NOVEL EVLP (N = 110)				
Recipient Age	Mean	SD	Median	Q1	Q3	IQR
<i>Years</i>	58.9	11.2	62.0	56.3	65.8	9.5
Recipient LAS	Mean	SD	Median	Q1	Q3	IQR
<i>Lung Allocation Score</i>	41.30	13.42	36.92	33.41	44.53	11.11
NOVEL Control Recipients		NOVEL Control (N = 116)				
Recipient Age	Mean	SD	Median	Q1	Q3	IQR
<i>Years</i>	58.6	11.4	61.5	54.8	66.3	11.5
Recipient LAS	Mean	SD	Median	Q1	Q3	IQR
<i>Lung Allocation Score</i>	42.74	13.05	38.56	33.85	46.76	12.91
UNOS Control Recipients		UNOS Control (N = 4898)				
Recipient Age	Mean	SD	Median	Q1	Q3	IQR
<i>Years</i>	57.5	12.3	61.0	53.0	66.0	13.0
Recipient LAS	Mean	SD	Median	Q1	Q3	IQR
<i>Lung Allocation Score</i>	45.7	15.2	40.5	34.9	50.0	15.1

There were more Fibrosis and Emphysema/COPD/Alpha1 patients in the EVLP arm versus the control arm as well as more Single Lung Transplants in the EVLP arm versus the Control arm, however these findings were not statistically different at a 0.05 threshold for significance.

10.4.3. Evaluation of EVLP Transplanted and Non Transplanted

Table 24: Post-EVLP Data		
EVLP Run Data	NOVEL EVLP	
	Not Transplanted N = 106	Transplanted N = 110
Best PO2		
<i>Best PaO2 (Mean)</i>	98.4	102.0
<i>Best PaO2 (Median)</i>	92.5	91.0
<i>Best Δ PO2 (Mean)</i>	327.9	418.5
<i>Best Δ PO2 (Median)</i>	340.0	417.5
Key Parameters Influencing Decision to Transplant		
<i>Median PAP (mmHg)</i>	7.5	7.8
<i>Median LAP (mmHg)</i>	4.0	4.0
<i>Median PVR (mmHg)</i>	219.5	185.5
<i>Median CStat (dynes)</i>	85.0	103.0
<i>Median PaO2 (Median)</i>	84.0	82.0

The table shows that pulmonary artery pressures, left arterial pressures and pulmonary vascular resistance, although valuable information, were not significant by themselves in determining whether the lung was transplantable. The best predictor of a transplantable lung was a combination of compliance (CStat information obtained from the XPS™ ventilator) and POR2R combined with the clinical discretion of the clinical team.

10.5. Long Term Data

10.5.1. Long Term Survival (All Cause Mortality)

Table 25: Survival at 1, 2 and 3 Years							
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.	

The table shows there is no statistically significant difference in 2 and 3-year survival between the EVLP and Control and UNOS Control arms.

10.5.2. Long Term Pulmonary Function Tests

Table 26: Pulmonary Function Test - FEV1 at 1, 2, 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
<p>* Only living subjects who had reached the 2/3 year timepoint were not included in the analysis.</p> <p>** 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 tracheated or hospitalized at the scheduled time of evaluation.</p>						

The table demonstrates similar PFT function between the EVLP and Control arms at 2 and 3 years.

10.5.3. Long-Term Bronchiolitis Obliterans Syndrome

Table 27: 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.				

The table demonstrates similar BOS outcomes between the EVLP and Control arms at 1, 2, and 3 years.

10.6. DCD Utilization Increase

- 110 patients underwent lung transplant using initially unacceptable donor lungs that were reassessed after EVLP treatment (up to 6 hours) using the XPS System™ with Steen Solution™.
- Match run data demonstrated that most lungs were rejected prior to being offered for EVLP.
- 68 DCD donors were placed on EVLP with 28 being transplanted. The NOVEL study had 14 centers that transplanted DCD donors, only 2 of these 14 centers had experience transplanting DCD donors prior to EVLP. The use of the EVLP technology has prompted these 12 other centers to start a DCD program at their institutions.

10.6.1. Match Run Data

Table 28: Key for Match Run Tables

*	Indicates if lungs were refused by other transplant centers due to poor quality. Yes, means Poor Lung Quality all other reasons are listed in table. If listed as UNK they were listed Provisional Acceptance but no reason listed for why they did not take the lung.
**	Indicates the position on the Donor Net list where the recipient fell. For example, the sequence for Donor 1002 was 30, meaning 29 recipients above this patient were refused by their respective transplant centers and the 30th recipient was accepted for transplant only post-EVLP.
***	Indicates how many additional recipient centers beyond the EVLP center were contacted by the OPO. This is an indication of how many other transplant centers refused the organ before the offering OPO made the decision to stop placement efforts and send the lungs to the EVLP center.
****	Indicates how many regions past the local donor center were contacted by the offering OPO. Region A is 500 miles away from the donor hospital, Region B is 1000 miles, Region C is 1500 and D is 2000 miles.

Table 29: Lung Match Runs For all EVLP Transplanted Donor Lungs

UNOS Encrypted Donor ID	Rejections due to "Poor Lung Quality" *	Recipient Match Sequence **	Match Attempts by OPO ***	Furthest Zone Attempted ****
1002	YES	30	57	A
1006	YES	15	51	B
1008	YES	9	40	B
1011	YES	1	6	LOCAL
1013	YES	1	173	A
1014	YES	1	15	A
1018	YES	41	42	A
1020	NO-no serum for Xmatching	1	43	B
1027	YES	11	20	A
1028	YES	9	19	LOCAL
1030	YES	3	13	LOCAL
1033	YES	2	18	A
1036	YES	3	3	A
1037	YES	29	34	B
1039	YES	59	59	A
1041	YES	66	383	B
1043	YES	1	9	A
1044	YES	4	10	A
1047	YES	16	165	A
1048	YES	9	17	A
1049	YES	72	84	A
1051	YES	2	2	LOCAL

Table 29: Lung Match Runs For all EVLP Transplanted Donor Lungs				
UNOS Encrypted Donor ID	Rejections due to "Poor Lung Quality" *	Recipient Match Sequence **	Match Attempts by OPO ***	Furthest Zone Attempted ****
1053	UNK	1	1	LOCAL
1054	YES	10	156	A
1058	YES	11	59	A
1059	YES	4	26	A
1060	YES	38	56	A
1061	YES	26	75	D
1064	YES	4	6	A
1065	YES	73	73	A
1068	YES	2	13	A
1069	YES	2	17	A
1072	YES	5	21	A
1073	YES	5	29	A
1076	YES	8	16	A
1078	YES	3	31	A
1079	YES	2	98	A
1081	YES	3	17	A
1084	YES	2	129	A
1086	YES	UNK	4	A
1087	YES	28	103	A
1090	YES	40	44	A
1091	YES	32	33	A
1095	YES	99	99	B
1098	YES	2	2	LOCAL
1099	YES	60	97	A
1100	YES	11	48	A
1101	YES	14	169	B
1102	YES	134	134	A
1103	YES	6	24	LOCAL
1106	YES	25	158	B
1110	YES	4	63	D
1112	YES	3	79	LOCAL
1113	NO-Directed Donation	24	24	LOCAL
1115	YES	147	163	A
1116	YES	57	76	A
1118	YES	5	32	LOCAL
1119	YES	24	54	A
1124	YES	13	35	LOCAL
1127	YES	7	16	LOCAL
1128	YES	11	20	LOCAL
1129	YES	13	41	LOCAL
1130	YES	104	104	A

Table 29: Lung Match Runs For all EVLP Transplanted Donor Lungs				
UNOS Encrypted Donor ID	Rejections due to "Poor Lung Quality" *	Recipient Match Sequence **	Match Attempts by OPO ***	Furthest Zone Attempted ****
1133	YES	14	17	A
1139	YES	1	23	B
1141	YES	14	34	LOCAL
1142	YES	3	17	LOCAL
1143	YES	22	79	B
1144	YES	2	25	B
1146	YES	3	38	B
1149	YES	11	35	B
1150	YES	5	8	B
1152	UNK	1	25	LOCAL
1154	UNK	1	41	A
1155	YES	116	126	B
1156	YES	3	30	D
1157	YES	1	48	A
1159	YES	29	299	B
1161	YES	6	6	LOCAL
1162	YES	3	3	LOCAL
1163	YES	7	7	LOCAL
1164	YES	4	10	A
1167	YES	37	40	A
1168	YES	49	56	A
1169	YES	49	130	A
1170	YES	29	48	A
1171	YES	14	16	A
1172	YES	21	21	A
1173	YES	3	9	A
1174	YES	7	12	A
1178	YES	15	20	LOCAL
1179	YES	8	14	A
1183	YES	5	6	LOCAL
1185	NO-No serum for Xmatching	1	4	A
1186	YES	9	18	A
1187	YES	26	50	A
1189	YES	24	61	A
1191	YES	5	30	A
1194	YES	33	33	A
1199	YES	16	28	B
1201	YES	20	34	A

One determination of the efficacy of the EVLP method is to show that the EVLP method is able to safely add useable lungs into the donor pool. A custom report was run by UNOS on the donors of organs used for EVLP in the NOVEL trial. Almost 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. Two lungs were rejected due to no serum being available for crossmatching, one was a directed donation, and for 10 there was no reason listed on match run. In both of the tables below, the point at which the OPO decided to stop placement efforts and revert to an EVLP Center is shown. The tables are divided between the lungs placed on EVLP and eventually transplanted and for EVLP lungs not transplanted. For both groups combined (n=202) the OPOs made an average of 23, (median 9, range 1-199) placement attempts before a site said yes to the organ. According to Cantu, et al., 70% of organs are placed by match sequence number 10. For most lungs, the OPO continued to attempt placement after an EVLP site had said yes to taking the lung and placing on EVLP in order to place it at a non EVLP site. This was due to the fact that 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. The average number of times that the lung was offered in this total group was 53, (median 32, range 1-383 times). Of those lungs where there was both match data and post-match data available the average number of times the lung was offered after an EVLP site agreed to take the lung was 30 (median 23, range 0-317). In other words, without the option of EVLP, the OPO would have stopped lung placement efforts at the last Match Attempt listed and these lungs would have not been used for transplant.

The following table (Table 28) summarizes the lung match placement efforts for donor lungs receiving EVLP, but not transplanted due to worsening function. There are more unknowns (UNK) listed for this group. When UNOS was questioned about this, their summation was that because OPO's are not audited for organs that are not transplanted that the OPO did not go back and update the donor match run with who eventually received the donor lung into the UNOS database.

Table 30: Lung Match Runs For all EVLP NOT Transplanted Donor Lungs				
UNOS Encrypted Donor ID	Rejections due to "Poor Lung Quality" *	Recipient Match Sequence **	Match Attempts by OPO ***	Furthest Zone Attempted ****
1001	YES	UNK	27	A
1003	YES	199	233	A
1004	YES	UNK	7	Local
1005	YES	72	73	D
1007	YES	UNK	18	B
1009	YES	UNK	2	Local
1010	YES	UNK	1	Local
1012	YES	UNK	3	Local
1015	YES	UNK	43	A
1016	YES	9	12	A
1017	YES	6	24	A
1019	YES	6	7	A
1021	YES	9	45	A
1022	YES	3	6	A
1023	YES	9	20	B
1024	YES	6	11	A
1025	YES	3	13	Local
1026	YES	UNK	23	Local
1029	YES	9	16	Local

Table 30: Lung Match Runs For all EVLP NOT Transplanted Donor Lungs				
UNOS Encrypted Donor ID	Rejections due to "Poor Lung Quality" *	Recipient Match Sequence **	Match Attempts by OPO ***	Furthest Zone Attempted ****
1031	YES	1	8	Local
1032	YES	5	19	A
1034	YES	37	38	A
1035	YES	5	15	A
1038	YES	139	139	A
1040	YES	UNK	3	D
1042	UNK	UNK	12	Local
1045	UNK	UNK	7	A
1046	UNK	UNK	30	A
1050	YES	1	41	A
1052	YES	UNK	9	Local
1054	YES	10	156	A
1055	YES	UNK	17	Local
1056	YES	4	34	A
1057	YES	1	20	A
1062	YES	37	45	B
1063	YES	30	49	B
1066	YES	UNK	228	B
1067	YES	37	113	D
1070	YES	2	116	A
1071	YES	4	14	A
1074	YES	UNK	16	A
1075	YES	UNK	22	A
1077	YES	UNK	16	A
1080	YES	UNK	127	A
1081	YES	3	17	A
1082	YES	UNK	7	A
1083	YES	UNK	15	A
1085	YES	16	23	B
1086	YES	UNK	4	A
1088	YES	3	115	D
1089	UNK	UNK	8	Local
1092	YES	114	158	A
1093	YES	UNK	65	A
1094	YES	UNK	79	A
1096	YES	UNK	17	A
1097	YES	UNK	37	A
1104	YES	UNK	128	B
1105	YES	UNK	80	A
1107	YES	UNK	85	A
1108	YES	UNK	138	A
1109	YES	UNK	81	Local

Table 30: Lung Match Runs For all EVLP NOT Transplanted Donor Lungs				
UNOS Encrypted Donor ID	Rejections due to "Poor Lung Quality" *	Recipient Match Sequence **	Match Attempts by OPO ***	Furthest Zone Attempted ****
1111	YES	UNK	69	A
1114	YES	UNK	95	A
1117	YES	UNK	37	A
1120	YES	UNK	47	A
1121	YES	UNK	47	A
1122	YES	UNK	37	A
1123	YES	16	20	A
1125	YES	UNK	52	A
1126	YES	UNK	38	Local
1131	YES	33	45	A
1132	YES	55	55	A
1134	YES	24	27	A
1135	YES	18	43	A
1136	YES	UNK	376	B
1137	YES	54	55	B
1138	YES		19	B
1140	YES	176	176	B
1145	UNK	UNK	100	B
1147	YES	UNK	78	B
1151	YES	UNK	28	Local
1153	UNK	UNK	27	Local
1158	YES	8	11	A
1160	YES	UNK	133	A
1165	YES	2	18	Local
1166	YES	UNK	12	A
1175	YES	1	15	A
1176	YES	UNK	40	A
1177	UNK	UNK	43	A
1180	YES	UNK	33	A
1181	YES	UNK	8	A
1182	YES	UNK	10	Local
1188	YES	2	272	A
1190	YES	UNK	14	A
1192	YES	UNK	41	A
1193	YES	UNK	24	C
1195	YES	UNK	17	A
1196	YES	UNK	18	A
1197	YES	UNK	17	C
1198	YES	UNK	210	B
1200	YES	12	33	A

Using all available data in this group(n=101), the average attempts to a match in Group 2 was 29 (median 9, range 1-199). The number of total attempts was an average of 53 (median 28, range 1-

376). With those IDs that had both match data and attempts (n=41) the average number of times that a match was attempted after being accepted, was 33 (median 15, range 0-270).

Note: Information presented in the above two tables is based on data as of April 20, 2018. Data are subject to change based on future data submission or correction. These data are provided by TII, a subsidiary of UNOS, as requested by XVIVO Perfusion, Inc.

11. CONCLUSION

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%).

To further explore these findings with respect to the selection bias in the control arm for this co-primary endpoint, post-hoc analyses were performed by XVIVO comparing the EVLP data to data from the UNOS registry.

The NOVEL and NOVEL Extension trial data were analyzed using the post-hoc 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. Furthermore, the long-term survival of the EVLP and NOVEL Control arms are not significantly different as demonstrated by the 2-year (EVLP 83%, NOVEL Control 87%, UNOS 79%) and 3 year (EVLP 70%, NOVEL Control 77%, UNOS 71%) survival data.

An additional post-hoc analysis on the UNOS dataset was performed on the next available "control," or the next available transplanted patient who met study inclusion/exclusion criteria. Taking into consideration the inherent limitations of a retrospective, post-hoc analysis, the 1-year survival for that cohort was 89% which was similar to the EVLP arm 86%.

For the 72-hour PGD Grade 3 co-primary endpoint, a comparison between the EVLP and Control Groups 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 PGD3 at 72 hours was made between the EVLP Group and LTOG dataset. Taking into consideration the inherent limitations of a retrospective, post-hoc analysis, the EVLP arm (16%) demonstrated a similar PGD Grade 3 rate at 72 hours post-transplantation to the published LTOG rate (16.8%) from Diamond, et al.

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 Arm 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 LAS.

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.

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

As an attempt to answer remaining questions from the NOVEL/NOVEL Extension study, a post-approval study (PAS) will be performed.

12. REFERENCES

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