

Clinical Trial Protocol: EVP-DEV-LTX-301

Study Title: Increasing Lung Transplant Availability Using Normothermic Ex Vivo Lung Perfusion (EVLP) at a Dedicated EVLP Facility

Study Number: EVP-DEV-LTX-301

Study Type: Pivotal

Product Name: Centralized Lung Evaluation System

IDE Number: G170312

Indication: Normothermic *ex vivo* evaluation of lungs for transplantation

Investigators: Multicenter

Sponsor: Lung Bioengineering Inc.

Medical Director: Jacqueline Honig, MD

Sponsor Contact: Michael Roberts

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Statement of Compliance

The study will be conducted in accordance with the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) (ICH E6), the Code of Federal Regulations (CFR) on the Protection of Human Subjects (21 CFR Part 50), the Investigational Device Exemption (IDE) requirements under 21 CFR 812, and the SPONSOR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

Confidentiality Statement

The concepts and information contained herein are confidential and proprietary and shall not be disclosed in whole or part without the express written consent of Lung Bioengineering, Inc.

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SYNOPSIS

Device	Centralized Lung Evaluation System (CLES)
Indication for Use	The CLES is intended to increase use of deceased donor lungs for transplant by enabling organ evaluation by normothermic perfusion and ventilation in a controlled environment outside the body (<i>ex vivo</i>). The device is intended for use with potential donor lungs not otherwise used for transplant into male and female patients aged 18 years or older with end-stage lung disease awaiting first-time (double or single) lung transplant. The CLES is intended for use exclusively by Lung Bioengineering Inc. in a Company-controlled facility. The CLES is not intended for use by any entity that is not a Company-controlled facility.
Study Objective	The objective of this study is to establish the safety and effectiveness of the CLES in enabling evaluation of potential donor lungs not otherwise used for transplant into subjects with end stage, survival-limiting lung disease in need of lung transplantation. This will be accomplished by evaluating subject survival at the later of 12 months or initial hospital discharge post-transplant.
Study Population	The study will be open to all eligible male and female patients, aged 18 years or older, with end-stage lung disease awaiting lung transplant at a participating Study Center. Subjects receiving either single lung transplant (SLT) or double lung transplant (DLT), will be enrolled in the study. No less than one-third of enrolled, matched subjects will have received a SLT or DLT.
Control Group	To compare “standard” safety, a matching control group will be identified from contemporaneous standard of care lung transplant recipients on a center by center basis. These subjects will be matched by LASDDG (underlying disease pathology), single or double lung transplant, and pre-transplant extracorporeal life support (e.g., ECMO, mechanical ventilation).
Study Design	This is a prospective, multicenter, un-blinded, non-randomized study evaluating the safety and effectiveness of the CLES. The study is designed as a pivotal study to provide data to support a Premarket Approval (PMA) application. The study will evaluate the safety of the CLES by tracking post-transplant survival in the EVLP Study Group. Standard safety measures will also be assessed for CLES and a matched contemporaneous control group. The study will evaluate the effectiveness of the CLES for the ability to evaluate lungs that would not otherwise be used for transplant directly from the deceased donor to a recipient by providing the transplant surgeon or physician an opportunity to assess if the lung(s) is/are suitable for transplantation. The Study database will be locked for analyses of endpoints after the last subject completes his/her last Study Center visit at 12 months (or initial hospital discharge, if later) and all on-going SAEs or AEs have been followed as specified per protocol.
Subject Inclusion Criteria	Each patient must meet all of the following criteria to be enrolled in the Study: 1. 18 years of age or older. 2. Male or female. 3. Patient actively awaiting a single or double lung transplant. 4. Patient or patient’s representative provides informed consent for participation in the study prior to participating in any study-related assessments or procedures. 5. Patient matches with and undergoes a transplant with a donor lung.

Subject Exclusion Criteria	Patients who meet any of the following criteria will be excluded from the study: 1. Patients listed for same-side lung re-transplantation. 2. Patients listed for multiple organ transplantation including lung and any other organ. 3. Patients listed for live donor lobar lung transplant. 4. Patients positive for human immunodeficiency virus (HIV) or <i>Burkholderia cenocepacia</i> infection. 5. Patient receives a standard of care (non-EVLP) lung transplant but does not match to an EVLP subject based on the criteria for control matching. 6. Transplanted with a lung that was perfused using another EVLP technology. 7. Participating in another respiratory or cardiovascular clinical trial.
Primary Endpoint	Post-transplant survival measured as the combined incidence of twelve month mortality and mortality prior to first hospital discharge after the lung transplant procedure.
Secondary Endpoints	The following secondary endpoints will be evaluated for the EVLP and Control Groups: 1. Adjudicated lung graft-related mortality measured as the percentage of study subject deaths determined to be related directly or indirectly to the transplanted organ; 2. Subject survival at 30 days post-transplant; 3. Subject survival at 90 days post-transplant; 4. Subject survival at 6 months post-transplant; 5. Subject survival at 12 months post-transplant; 6. PGD Score (Grades 0-3) measured at 0, 24, 48 and 72 hours post-transplant; 7. Duration of subject ventilator support, measured as total number of hours post-transplant where ventilator support is required prior to initial hospital discharge; 8. Rate of ECMO use post-transplant measured as the proportion of subjects that require ECMO support for any reason and at any time prior to initial hospital discharge after transplantation; 9. Intensive care unit (ICU) length of stay (LOS), measured as total number of days post-transplant in the ICU until first hospital discharge, inclusive of ICU readmissions during the initial transplant hospitalization; 10. Hospital LOS measured as total number of days in the hospital until first discharge post-transplant; 11. Extended evaluation and preservation time, defined as the elapsed time between donor aortic cross clamp at procurement and placement of the first stitch in the anastomosis at transplant. This time is recorded separately for each lung transplanted in a double lung procedure; 12. Assessment of the overall safety of CLES lung transplants during each subject's participation in the study, as reported through adverse events (AEs); 13. Rate of Chronic Lung Allograft Dysfunction (CLAD) measured as percentage of subjects diagnosed with CLAD post-transplant; 14. Rate of respiratory failure; and 15. FEV₁ values at defined timepoints.

	The following secondary endpoints will be evaluated for the EVLP Group only: 16. Utilization rate of EVLP lungs measured as the number of EVLP procedures resulting in lungs accepted for transplant divided by the number of EVLP procedures performed on lungs referred for EVLP; 17. Increase in use of donor lungs measured by the number of lungs referred for EVLP and accepted for transplantation at a Study Center without the use of EVLP;
Study Intervention	EVLP is a novel technology that permits the evaluation of lungs through normothermic perfusion and ventilation. Organ procurement organizations (OPOs) allocate lungs nationally to a patient waitlisted by a Transplant Center based on geographical proximity to the donor hospital, and by each patient's specific Lung Allocation Score (LAS). At the time of lung allocation, Transplant Centers review relevant data collected by the OPO to best select a potential donor lung, and to accept or decline an offer for each given eligible recipient. Accepted offers result in the dispatch of a surgical team to procure the lungs from the donor hospital. EVLP technology can provide Transplant Centers with an additional resource, allowing evaluation of potential donor lungs that would not otherwise be used for transplant. The decision to consider EVLP provides an additional evaluation opportunity, since centers will dispatch a lung procurement team to the donor site. Standard intraoperative recruitment maneuvers may identify lungs appropriately taken directly from the donor for transplantation to the center recipient without EVLP. At the same time, the team may decide to proceed with a plan for the lungs to undergo EVLP (e.g. if <i>in situ</i> recruitment efforts are unsuccessful). Upon retrieval, donor lungs selected for EVLP, will be packaged and transported to the Sponsor's EVLP facility. The EVLP procedure will be performed by specifically trained Ex Vivo Lung Specialists. The Sponsor will perform the EVLP procedure using the CLES for up to 6 hrs, collecting and relaying lung function data hourly, or more frequently as requested by the Study Center Investigator/team. Additionally, the Study Center Investigator will have access to remote monitoring capabilities at the Sponsor EVLP Center through a dedicated audio/video link. Final suitability decisions regarding transplantation reside with the Study Center Investigator. The preservation time for the first lung being transplanted (e.g. from donor lung retrieval to the end of CIT-2) must not be greater than a combined 22 hrs within individual phase limits as follows: $(\leq 10 \text{ hrs CIT-1}) + (3 - 6 \text{ hrs EVLP}) + (\leq 6 \text{ hrs CIT-2}) \leq 22 \text{ hrs}$ Preservation time for the second lung being transplanted from donor lung retrieval to the end of CIT-2 must not be greater than a combined 26 hrs within individual phase limits as follows: $(\leq 10 \text{ hrs CIT-1}) + (3 - 6 \text{ hrs EVLP}) + (\leq 10 \text{ hrs CIT-2}) \leq 26 \text{ hrs}$
Study Duration	Data will be collected from the organ donor, EVLP procedure, and enrolled subjects from the time of lung transplantation, then to 12 months post-transplant for the purposes of this study. The study duration from first patient, first visit (FPFV) to last patient, last visit (LPLV) prior to database lock is expected to be 36 months. Subsequently, data will be requested for all subjects from the Federal OPTN database for five years post-transplant to document long term survival and safety events.

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Lung Bioengineering Inc.
28 JAN 2021

Study Assessments	Medical History and Physical Examination will be documented at Baseline (day of transplant). Subject survival, PFTs, oxygenation status, Quality of Life measures, lung graft dysfunction and adverse events will be assessed at defined intervals from Baseline through 12 months post-transplant. PGD Score will be determined for each Subject by the Investigator Team at Baseline (Day 0, upon admission to the ICU after transplantation), as well as 24, 48, and 72 hrs afterward. Subject arterial blood gases and x-rays must be performed by the Investigator in order to calculate PGD Score.
Data Collection	A 21 CFR Part 11 compliant Electronic Data Capture (EDC) system will be used to collect data.
Statistical Methods	The primary analysis will be to calculate the posterior probability of the 12 month survival rate greater than the performance goal of 81.2%, the primary objective will be achieved if the posterior probability is greater than 0.95. Descriptive statistical analyses will be performed on the secondary endpoints for the EVLP and Control Groups. These analyses will include rate of survival and relative risk of death at 30 days, 90 days, 6 months, and 12 months post-transplant. Subjects selected through a matched contemporaneous Control Group will serve as a reference population for safety measures.
Number of Investigational Sites	Up to 16 Transplant Centers

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABG	Arterial Blood Gas
ADL	Activities of daily living
AE	Adverse Event/Adverse Effect
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CI	Confidence interval
CIT	Cold ischemic time
CLAD	Chronic Lung Allograft Dysfunction
CLES	Centralized Lung Evaluation System
CMX	Case Management Exchange
CRF	Case Report Form
CRO	Contract Research Organization
Cstat	Static compliance
DCD	Donation after Circulatory (Cardiac) Death
DLT	Double-lung Transplant
DMC	Data Monitoring Committee
ECLS	Extracorporeal life support
ECMO	Extracorporeal Membrane Oxygenation
EDC	Electronic Data Capture
EVLV	Ex Vivo Lung Perfusion
FDA	Food and Drug Administration
FEV ₁	Forced expiratory volume in one second
FiO ₂	Fraction of inspired oxygen
FPFV	First patient, first visit
GCP	Good Clinical Practice
GERD	Gastroesophageal Reflux Disease
HIV	Human immunodeficiency virus
hrs	Hours
IBW	Ideal Body Weight
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
ID	Identification

IDE	Investigational Device Exemption
IRB	Institutional Review Board
ISHLT	International Society for Heart and Lung Transplantation
LAP	Left atrial pressure
LAS	Lung Allocation Score
LASDDG	Lung Allocation Score Disease Diagnosis Group
LOS	Length of stay
LPLV	Last patient, last visit
mAwP	Mean airway pressure
MedDRA®	Medical Dictionary for Regulatory Activities
Min	Minutes
N	Number (typically refers to subjects)
OPO	Organ Procurement Organization
OPTN	Organ Procurement and Transplantation Network
OR	Operating Room
PAF	Pulmonary arterial flow
PaO ₂	Partial pressure of oxygen in arterial blood
PAP	Pulmonary arterial pressure
PawP	Peak airway pressure
PCO ₂	Carbon dioxide partial pressure
PGD	Primary Graft Dysfunction
PGD3	Primary Graft Dysfunction Grade 3
platAwP	Plateau Airway Pressure
PO ₂	Oxygen partial pressure
PvO ₂	Partial pressure of oxygen in venous blood
PVR	Pulmonary Vascular Resistance
QA	Quality Assurance
QC	Quality Control
RSI	Reference Safety Information (RSI)
SAE	Serious Adverse Event/Serious Adverse Effect
SAP	Statistical Analysis Plan
SD	Standard deviation
SLT	Single-lung Transplant
SOC	System Organ Class
SRTR	Scientific Registry of Transplant Recipients

T72	72 hours post-transplant
TES	Toronto EVLP System
TGH	Toronto General Hospital
UADE	Unanticipated Adverse Device Effect
UNK	Unknown
UNOS	United Network for Organ Sharing
US	United States
WHO	World Health Organization
WIT	Warm ischemic time

1 INTRODUCTION

1.1 LUNG TRANSPLANTATION AND EX VIVO LUNG PERFUSION BACKGROUND

Lung transplantation is often the only available therapy for patients suffering end-stage lung disease, and the number of patients who can appropriately benefit by lung transplantation far exceeds the number of donor lungs available. Importantly, the mismatch between demand for transplantable lungs and the supply of available organs is substantially higher than other solid organs, with the lungs being used for transplantation among only 24% of brain dead donors of other solid organs.[OPTN 2020]

It has been suggested that over 40% of the lungs rejected by the United States (US) lung transplant programs could have been transplanted if better information was available at the time of procurement.[Ware 2002] Technologies such as Ex Vivo Lung Perfusion (EVLP) might facilitate assessment of lung condition, thereby enabling transplant programs to use lungs for transplant that are currently discarded.

Steen et al., described an *ex vivo* perfusion technique in 2001, seeking to better evaluate lungs from non-heart beating donors (Donation after Circulatory Death [DCD]).[Steen 2001]. This method demonstrated the proof-of-concept that donor lungs could be assessed *ex vivo*, then successfully transplanted, initially into large animals, and later into humans.

Keshavjee's group in Toronto extended those observations, applying a modified, normothermic (37°C) EVLP technique using an acellular, albumin-based solution (STEEN Solution™), lower perfusion flow rates (40% of normal cardiac output), and a protective ventilation strategy to permit longer perfusion with excellent physiologic function after transplantation.[Cypel 2008a; Cypel 2008b; Cypel 2009] The "Toronto EVLP Method" was demonstrated as technically feasible and safe, permitting perfusion of donor lungs for up to 6 hours (hrs) in clinical practice.

1.1.1 Toronto Clinical Experience

The Human *Ex Vivo* Lung Perfusion (HELP) trial was a prospective, non-randomized, single-center study of outcomes of lungs not meeting conventional lung donor criteria, receiving 4 hrs of extended evaluation and preservation using EVLP. The EVLP treated lungs were compared to all other lungs transplanted at that transplant center (Control) during the same time period. In

addition to the 4 hrs of additional preservation time, EVLP -treated lungs received an obligatory second cold ischemic period during transport after completion of *ex vivo* evaluation.

The initial study results demonstrated that transplantation of donor lungs that were physiologically stable during 4 hrs of EVLP, resulted in similar outcomes to those obtained with conventionally procured and hypothermically-treated lungs.[Cypel 2011a]

Taken together, more than 300 donor lung sets have been evaluated by the Toronto group with a consistent increase in the lung utilization rate approximating 75%.[M Cypel, personal communication]. Overall, one-, three-, and five -year outcomes after lung transplantation have been similar to results obtained among lung recipients who received standard lung transplants without using EVLP.[Cypel 2011a; Cypel 2011b; Cypel 2012; Tikkanen 2012; Munshi 2013; Cypel 2013] Specifically, the 12 month survival rate for subjects who received lung transplants using EVLP from 2016 to 2018 was 82.5%, and the 12 month survival rate for subjects in the non-EVLP group during this time period was 85.7%.[M Cypel, personal communication]

1.1.2 Sponsor Clinical Experience: Centralized Lung Evaluation System

In 2015, Lung Bioengineering Inc (the Sponsor) began its clinical investigations under a traditional feasibility protocol, PXUS 14-001 (IDE #G140021), a prospective, multicenter, open-label study to evaluate the safety of the Centralized Lung Evaluation System (CLES) with lungs that did not meet standard lung donation criteria, or were otherwise unable to be used for traditional transplantation. [Lung Bioengineering 2020] The CLES is identical to the equipment used by the Toronto group in terms of system components used and operational protocol observed during EVLP. The primary endpoints of this study were rate of Primary Graft Dysfunction (PGD) Grade 3 at 72 hrs post-transplant and 30 day mortality. The results of this study suggest acceptable rates of PGD3 at 72 hrs and no 30 day mortality. Furthermore, similar outcomes in terms of post-transplant subject and graft survival at longer post-transplant timepoints were observed compared to a contemporaneous Control group. The 12 month survival rate for subjects in the feasibility study was 89.4% and the 12 month survival rate for the contemporaneous control group was 92.6%.

1.1.3 Report of Prior Investigations

A full report of prior investigations detailing the above and other EVLP studies will be provided to the Study Center Investigators and submitted to each reviewing IRB.

1.2 POTENTIAL RISKS AND BENEFITS

For many patients who choose evaluation and listing for lung transplantation, the inherent risks are outweighed by the benefit that transplantation is the only life prolonging therapy for end-stage lung disease. Factors underlying the exaggerated imbalance between lung donor supply and recipient mismatch compared with other solid organs have been reviewed earlier. EVLP -specific potential risks and benefits are presented below.

1.2.1 Potential Risks

The specific additional risks associated with EVLP beyond those encountered in lung transplant generally include extending preservation beyond that experienced using standard cold storage, the potential for contamination resulting from additional handling and manipulation of the lungs, and potential lung damage that might result from the normothermic evaluation process and associated procedures, such as cannulation, bronchoscopy, repackaging, etc. Although these risks were not observed in the Sponsor's Feasibility Study [Lung Bioengineering 2020], specific risks and mitigation strategies are addressed in the Risk Analysis. Additionally, although the study was not statistically powered to detect differences between groups for other post-transplant outcomes, the data do suggest possible trends related to transplanting lungs that would otherwise not have been used, such as increased time to first extubation, and ICU and hospital lengths of stay in the EVLP group.

1.2.2 Potential Benefits

1.2.2.1 Consistency in Lung Evaluation

Evaluation of lung and recipient risk profiles is based largely on the individual experience of the transplanting surgeon, which varies program-to-program, and this may become more important when transplanting lungs that would otherwise not have been used, including those from unconventional or Donation after Circulatory Death (DCD) donors. *Ex vivo* evaluation at the Sponsor's dedicated EVLP facility can therefore add a level of consistency (and potentially safety) in lung evaluation, possibly removing some of the variability between centers and

surgeons. The additional expertise provided by the Sponsor's specifically trained EVLP team can help the transplant teams evaluate the risk profile of an EVLP lung in context of the risk profile of a potential recipient. Additionally, the CLES offers the ability to conduct the evaluation with fixed hemodynamics outside of the confounding influence of the pathophysiology resulting from brain death and accompanying somatic injury in the donor.

1.2.2.2 Increased Donor Lung Use

Strategies which increase use of lungs from currently available donors provide the most immediate opportunity to increase availability for end stage patients currently awaiting transplantation. In 2016, there were 9,771 eligible donors recorded in the US and a total of 2,327 lung transplants, resulting in a donor lung use rate of 24% [OPTN 2020]. To date, despite targeted campaigns to increase public awareness of the importance of organ donation, the annual number of donors has increased very slowly. Therefore, novel technologies to increase donor lung use such as the CLES are needed to address the imbalance between donors and patients awaiting lung transplant. EVLP is anticipated to increase the number of donor lungs used for transplantation by enabling additional evaluation of organ function.

1.2.2.3 Shorter Recipient Waiting Times

Because EVLP may result in making more lungs available for transplantation, an additional potential benefit to lung candidates listed at a center participating in this study could be shorter waiting times for patients in need.

2 STUDY OBJECTIVES

This study will generate safety and effectiveness data on the ability of the CLES to provide an evaluation platform to a Transplant Center for lungs that would not otherwise be used for transplant. This information will be used to support a Premarket Approval Application to the FDA.

2.1 PRIMARY OBJECTIVE(S)

The primary objective of this study is to establish the safety and effectiveness of the CLES for enabling the evaluation of lungs intended for transplant into subjects with end stage, survival-

limiting lung disease in need of lung transplantation. This will be accomplished by determining subject survival at the later of 12 months or first hospital discharge post-transplant.

2.2 SECONDARY OBJECTIVE(S)

The secondary objectives of this study are to collect additional effectiveness and safety data in lung transplant subjects receiving donor lung(s) evaluated via the CLES by assessment of:

- Adjudicated lung graft-related mortality measured as the percentage of study subject deaths determined to be related directly or indirectly to the transplanted organ;
- Utilization rate of EVLP lungs measured as the number of EVLP procedures resulting in lungs accepted for transplant divided by the number of EVLP procedures performed on lungs referred for EVLP;
- Increase in use of donor lungs, measured by the number of lungs referred for EVLP and accepted for transplantation at a Study Center without the use of EVLP;
- Subject survival at 30 days, 90 days, 6 months, and 12 months post-transplant;
- PGD Score (Grades 0-3) measured at 0, 24, 48 and 72 hours post-transplant;
- Duration of subject ventilator support, measured as total number of hours post-transplant where ventilator support is required prior to initial hospital discharge;
- Rate of Extracorporeal Membrane Oxygenation (ECMO) use post-transplant, measured as the proportion of subjects that require ECMO support for any reason and at any time prior to initial hospital discharge after transplantation;
- Intensive care unit (ICU) length of stay (LOS), measured as total number of days post-transplant in the ICU until first hospital discharge, inclusive of ICU readmissions during that hospitalization;
- Hospital LOS measured as total number of days in the hospital until first discharge post-transplant;
- Extended evaluation and Preservation time, defined as the elapsed time between donor aortic cross clamp at procurement and placement of the first stitch in the anastomosis at transplant. This time is recorded separately for each lung transplanted in a double lung procedure;
- Assessment of the overall safety of CLES lung transplants during each subject's participation in the study, as reported through adverse events;
- Rate of diagnosis of Chronic Lung Allograft Dysfunction (CLAD) measured as number of subjects diagnosed with CLAD post-transplant;
- Rate of respiratory failure; and
- FEV₁ values at defined timepoints.

The above information will also be collected on subjects enrolled in a contemporaneous control group to evaluate similar findings among recipients of lungs not evaluated during EVLP.

3 INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN

This is a prospective, multi-center, unblinded, non-randomized, pivotal study to evaluate the effectiveness and safety of the CLES among subjects undergoing lung transplant using lungs after EVLP performed exclusively by the Sponsor at a Sponsor facility. The study will include male and female adult lung transplant recipients, requiring a Single Lung Transplant (SLT) or Double Lung Transplant (DLT) who are at least 18 years of age. Subjects who have signed informed consent (Section 10.4), match to a donor lung offer through the standard Organ Procurement and Transplantation Network (OPTN) allocation system, and meet the other eligibility criteria (Section 4), including matching with and undergoing a lung transplant may participate. Patients who consent for this study, but receive a conventional (i.e., non-EVLP) lung transplant will be considered for a contemporaneous control group matched to the EVLP treatment group. The control group will be Study Site specific to the EVLP group, then selected to best match recipients with respect to the following criteria: SLT/ DLT, Lung Allocation Score Disease Diagnosis Group (LASDDG), and pre-transplant ECMO. LASDDG is assigned according to OPTN Policy 10.1.F.i. [OPTN 2020] into one of four groups:

- Group A: Obstructive Lung Disease
- Group B: Pulmonary Vascular disease
- Group C: Cystic Fibrosis or Immunodeficiency Disorders
- Group D: Restrictive Lung Disease

If the subject is on ECMO at the time of lung allocation, a matching control subject would then be selected based on the above criteria in addition to their ECMO status at allocation.

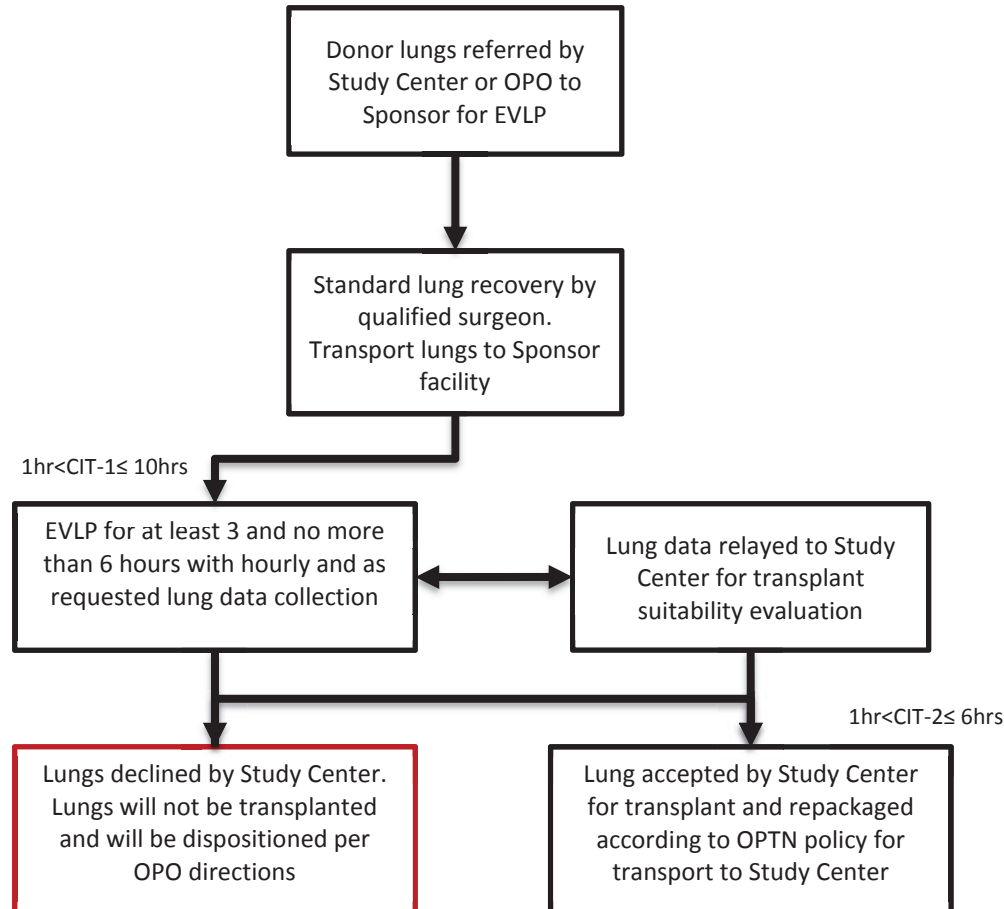
The goal is to provide a control group with similar characteristics and risks as the treatment group receiving EVLP. As an example, if a center enrolls a subject into the EVLP Group that received a double lung transplant, who had Pulmonary Fibrosis (DDG “D”), and was on ECMO support at the time of allocation, then that transplant center would be asked to provide a matching control subject from subsequent organ recipients who receive a standard of care double lung transplant, are categorized as LASDDG “D” due to an underlying restrictive lung disease, and were receiving ECMO at the time of allocation. Note: if a subject is placed on ECMO after

allocation but prior to surgery, this is not considered pre-transplant ECMO, and the matching control subject would not be matched based on “preventative” ECMO in these cases.

A maximum sample size of 93 EVLP Group subjects, receiving either SLT or DLT, is planned for this study. Also included will be 75 matched subjects who have received a conventional (i.e., non-EVLP) lung transplant and qualify for a contemporaneous control group (Control Group); no less than 50 matched subjects (25 EVLP and 25 Control) enrolled will have received a SLT or DLT. Enrolling an additional 18 subjects in the EVLP Group will provide more opportunities for Control Group matching, reducing the overall enrollment period in the study. The additional unmatched EVLP Group subjects’ data will be presented in the overall data set and will be used in the analysis of the primary endpoint.

Referral and evaluation of donor lungs for EVLP will follow the process outlined in [Figure 1](#) and detailed in Section [3.1.1](#).

Figure 1 Lung Referral and Evaluation Process



Once a donor lung is transplanted following EVLP, the eligible recipient, who has provided written informed consent, is enrolled into the study. The other patients from that Center, who have consented for the study, but who receive a conventional (non--EVLP) lung transplant, will be considered for inclusion in a contemporaneous control group. Selection of control patients will take place on a patient-by-patient basis, according to similarities with a patient receiving an EVLP treated lung. Investigators and their team will be notified by the Sponsor on a real-time basis of the specific matching criteria required for the next control subject from that Study Center (see Section 5.3). Each control subject must demonstrate similar “matching” to a subject enrolled in the Study from the same Center who received a lung transplant from a lung after EVLP, based on the following criteria:

- SLT versus DLT
- LASDDG

- ECMO status at the time of lung allocation

The post-intervention phase of the study includes follow-up visits through 12 months post-transplant or first hospital discharge post-transplant, whichever is later. The Study database will be locked for analyses of endpoints after the last subject completes his/her last Study Center visit at 12 months (or first hospital discharge, if later) and any required follow-up for Serious Adverse Events (SAEs) and Adverse Events (AEs).

Following transplantation, subjects will be admitted to the Intensive Care Unit (ICU), and the initial partial pressure of oxygen (PaO₂) will be recorded and a chest radiograph will be taken to establish a PGD Score. The data used to calculate a PGD Score will be recorded every 24 hrs for the next 72 hrs. The ICU discharge date will be documented. A final study visit will occur at 12 months (±30 days) post-transplant, or if the subject remains hospitalized without an initial hospital discharge beyond 12 months, a 12 month and a discharge visit will occur. However, data will also be collected on enrolled subjects at 30 days, 90 days and 6 months post-transplant. Subsequently, recipient data will be collected from the Federal OPTN database for five years post-transplant to monitor long term survival and safety events. Study assessments will be performed as outlined in the Schedule of Events ([Appendix 1](#)).

3.1.1 EVLP Procedure

3.1.1.1 Lung Referral

Donor lungs are allocated to transplant centers according to OPTN Policy 10. [OPTN 2020]
Once a potential organ donor, at or near death has been identified, the regional OPO is contacted to coordinate the organ donation. The Organ Procurement Organization (OPO) enters specific donor demographics into a national database, identifying individuals awaiting an organ transplant, and a match run list of patients for each organ is established. In match run order, the OPO then contacts the relevant transplant centers to offer each organ to a specific patient. The details of the donor's medical history and other relevant information is provided to the Centers for consideration. The transplant center, then has one hour to accept the lung for the specific matched patient, or the lung offer continues in match run sequence for consideration on behalf of additional patients until a center accepts the lung(s) for transplantation into a specific individual, the match run list is exhausted, or there are timing issues which may cause the OPO to suspend

or expedite subsequent lung offers. The lung acceptance by a center is based on several factors, but primarily upon the transplant center staffs' clinical judgement that a specific donor lung is suitable for the intended recipient. When the transplant center accepts, the lung is shipped to the transplant center for a "standard of care" transplant. For the purposes of this study, "standard of care" means a lung transplant that occurs without EVLP, and may include "extended criteria" or "marginal" donor organs that are routinely transplanted as a matter of acceptable clinical practice.

If the transplant center is also a Study Center in this trial, the potential to enroll a consented patient into this study may also emerge. The donor lung(s) could be considered for EVLP when the circumstances are appropriate. Similarly, as described, other consented recipients who receive lungs that have not undergone EVLP may be eligible for enrollment in the control group. Again, eligibility is based on meeting the overall study inclusion criteria, not meeting any exclusion criteria, and matching to an already enrolled EVLP recipient at that Study Center based on the criteria found in Section 5.3.

When a referred organ will not be used for standard of care transplantation, but meets the Study inclusion and exclusion criteria, a Study Center or OPO may refer the lung(s) to a Sponsor facility for EVLP. This decision is based on the protocol criteria as well as the medical expertise and judgement of the Study Center Investigator or OPO Medical Director in context of the details of the particular donor case. The Sponsor shall not make recommendations for referring an organ to the EVLP facility. The Sponsor will, however, verify that the inclusion/exclusion criteria for referred lungs are followed by the Study Center or OPO prior to accepting lungs for EVLP. The verification process will happen when the Study Center or OPO contacts the Sponsor to notify them that an organ has been referred for EVLP, and to discuss lung transportation logistics and other case details. If it is determined that an error has been made by the Study Center or OPO in determining study eligibility, the lung(s) will not be sent to the Sponsor for EVLP.

3.1.1.2 Lung Retrieval

Upon retrieval, donor lungs will be packaged and transported to a Sponsor EVLP facility, according to standard procedures, following OPTN Policy 16.[OPTN 2020] Upon arrival at the Sponsor's facility, lungs will be placed onto the CLES by a specifically -trained Ex Vivo Lung Specialist. Prior to starting EVLP, the estimated duration of CIT-1 will be confirmed to be less than or equal to 10 hrs.

The EVLP procedure will be performed by a dedicated EVLP team under remote video observation by the Study Center that accepts the organ for transplantation. The Sponsor will perfuse the lung using the CLES for up to 6 hrs, collecting and relaying lung function evaluation data hourly, or more frequently as requested by the Study Center physician. Additionally, the Study Center Investigator will have access to remote monitoring capabilities at the Sponsor EVLP Center for evaluating lung function data and monitoring the procedure through a dedicated audio/video link.

3.1.1.3 Lung Evaluation

EVLP begins once extracorporeal circulation is established in the potential donor lung(s). The EVLP procedure shall run for 3 to 6 hrs. At any time between 3 and 6 hrs of starting the procedure, the EVLP team, in consultation with the Study Center Investigator, can stop the evaluation, at which time the lung will be packaged for the Study Center or the procedure will be stopped without transplantation. The following perfusion parameters will be collected for internal monitoring:

- Pulmonary arterial pressure (PAP), mmHg
- Left atrial pressure (LAP), mmHg
- Pulmonary arterial flow (PAF), L/min
- Pulmonary Vascular Resistance (PVR), dynes x sec x cm-5 = $[PAP - LAP] \times 80 / PAF$.

Ventilation begins when the lung temperature reaches 32°C measured from the temperature probe connected to the heat exchanger. Then, before each hourly oxygen challenge, the ventilator should be set at a tidal volume of 10 mL/kg (based on donor ideal body weight [IBW]) for 5 min at a fraction of inspired oxygen (FiO₂) of 100% (1.0) prior to obtaining perfusate gas samples.

After the perfusate gas sample has been collected, the ventilator tidal volume is set back to the maintenance settings of 7 mL/kg and FiO₂ of 21% (0.21).

The following ventilation parameters will be measured and recorded hourly at the end of each oxygen challenge:

- Mean, peak and plateau airway pressure (mAwP, PAwP, platAwP), cm H₂O
- Static and dynamic compliance (mL/cm H₂O)
- Perfusate gas analysis at lung inflow and outflow: PO₂, partial pressure of carbon dioxide (PCO₂), pH, glucose, and lactate.

Other Evaluation Parameters

Bronchoscopy: A bronchoscopy may be performed following initial ventilation to clear the airways as indicated. Additional bronchoscopies can be performed upon request by the Study Center Investigator. All bronchoscopic evaluations will be recorded digitally and transmitted to the Study Center Investigator for review.

X-ray: A digital radiograph of the lung may be taken periodically during EVLP to detect edema, consolidations, or other abnormalities. The resulting image will be transmitted digitally to the Study Center Investigator for review.

Perfusate volume: Loss of perfusate volume within the perfusion circuit during EVLP, which may indicate loss of alveolar integrity, will be monitored and documented during the evaluation period.

3.1.1.4 Transfer of EVLP Data to the Study Center

Throughout the EVLP procedure, donor lung parameters are communicated by the EVLP Specialist for evaluation by the Study Center Investigator, who will make the final clinical determination of EVLP lung transplant suitability.

3.1.1.5 Acceptance of EVLP Lung for Transplant

The EVLP team, working with the Study Center Investigator will monitor and evaluate the EVLP procedure data remotely. Together, they will serve as a collaborative team regarding the

EVLP procedure, including the timing of the EVLP termination. Although the EVLP team is prepared to offer guidance, final decisions reside with the Study Center Investigator.

Upon acceptance of an EVLP donor lung by the Study Center, the single lung or lung block is cooled to 10°C.

The cessation of ex vivo perfusion and ventilation mark the start of CIT-2. The lung(s) is prepared for hypothermic storage by flushing with cold storage solution and tracheal clamping to maintain partial lung inflation. Accepted lung(s) will be repackaged by the Sponsor according to OPTN Policy 16 [OPTN 2020], stored on wet ice (approximately 4°C) in low potassium dextran cold storage solution and transported to the Study Center.

Preservation time for the first lung transplanted from donor lung retrieval to end of CIT-2 must not be greater than a combined 22 hours and individual phase limits as follows:

$$(\leq 10 \text{ hours CIT-1}) + (3 - 6 \text{ hours EVLP}) + (\leq 6 \text{ hours CIT-2}) \leq 22 \text{ hours}$$

Preservation time for the second lung transplanted in DLT procedures from donor lung retrieval to end of CIT-2 must not be greater than a combined 26 hours and individual phase limits as follows:

$$(\leq 10 \text{ hours CIT-1}) + (3 - 6 \text{ hours EVLP}) + (\leq 10 \text{ hours CIT-2}) \leq 26 \text{ hours}$$

EVLP lungs that exceed 10 hrs of CIT-1, or are perfused for less than 3 hrs or more than 6 hrs will not be used for transplantation. These lungs will be discarded, returned to the OPO or designee, or can be used for purposes other than transplantation, such as medical research, according to the responsible OPO's directions.

For any lung (single or double) that is used for transplantation and has a total preservation time (TPT) greater than 17 hours, the following data will be collected: first Cold Ischemic Time (CIT-1), second Cold Ischemic Time (CIT-2), TPT, PGD at 0, 24, 48, and 72 hours post-transplantation, and 30-day mortality. The Data Monitoring Committee (DMC) will review the study outcomes of these subjects and provide a report to the FDA.

Study enrollment will be initially limited to 10 subjects with total preservation times equal to or exceeding 17 hrs (measured for the first lung), although the study will be approved for the full cohort, as long as total preservation time is less than 17 hrs (measured for the first lung) in these subjects. Upon enrollment of 10 subjects with total preservation time ≥ 17 hours (measured for the first lung), the DMC will review the study outcomes of these subjects and a report will be submitted to FDA. If this report demonstrates favorable safety outcomes, this limitation may be removed.

First lung CIT-2 is the elapsed time between the end of the EVLP procedure and the start of the anastomosis, marking the beginning of the implantation phase of the transplant procedure. This CIT-2 may not exceed 6 hrs. Prior to shipping EVLP lungs to the Study Center, an estimated time of arrival will be calculated by the EVLP Specialist in consultation with the Study Center to ensure the criterion for CIT-2 will be met. Therefore, if the anticipated first lung CIT-2 will exceed 6 hrs due to logistical considerations (projected flight time and/or surgical staff schedule, etc.), the lungs shall not be transported to the Study Center. Similarly, if after leaving the EVLP facility, prolonged transport time or patient logistical or other issues compromise the ability to ensure actual first lung CIT-2 is less than or equal to 6 hours, the transplant should not proceed. Documentation of CIT-2 expiry will be provided with each organ shipped to a Study Center. However, if the time between the start of CIT-2 and the start of transplantation exceeds 6 hrs, a protocol deviation shall be documented on a Case Report Form (CRF) and shall be reported to the Sponsor. The reason for the delay and an assessment of the first lung's condition prior to transplant shall be recorded in the CRF. These subjects will continue enrollment in the study and will be followed as part of the EVLP Group.

After the end of CIT-2, the warm ischemic time (WIT) period then begins, which lasts until the lung is reperfused in the recipient. This time period is expected to be no longer than the typical WIT at each Study Center for standard lung transplants.

For DLT procedures, the second lung must remain in cold storage in low potassium dextran solution while the first lung implantation is being performed. The time of the start of transplant of the second lung after the first lung is implanted and the second lung WIT should be consistent with historical surgical experience for sequential DLT at each Study Center. However, if the time

between the end of EVLP and the placement of the first stitch in the anastomosis of the second lung exceeds 10 hrs, a protocol deviation shall be documented on a CRF and shall be reported to the Sponsor. The reason for the delay and an assessment of the second lung's condition prior to transplant shall be recorded in the CRF. These subjects will continue enrollment in the study and will be followed in the EVLP Group.

3.1.1.6 Request for Reallocation of Lungs after EVLP

In the event the initially accepting Study Center declines the lungs during or after completion of the EVLP evaluation, the EVLP Specialist must contact the coordinating OPO (the "host" OPO) and provide the following information:

- OPTN/UNOS donor identification number (ID#);
- Name of the transplant Study Center and Investigator declining lungs after EVLP;
- Reason the lungs were declined;
- Names of all other Study Centers participating in the clinical trial;
- Current status of the lung(s) (i.e., still on EVLP, packaged on ice, in transit); and
- Contact information for the EVLP Specialist on call for the specific case.

Sponsor personnel will recommend the host OPO resume lung allocation according to the OPO's internal policies and procedures, reminding the OPO of the Study Centers participating in the study, and stressing that the EVLP procedure is investigational, and potential recipients must have signed the EVLP trial informed consent prior to participating in any study-related assessments or procedures.

In the event the host OPO can reallocate the lungs to another participating Study Center, the host OPO will contact the EVLP Specialist, who will then contact the interested physician (Study Center Investigator) to facilitate Case Management Exchange (CMX) access and information exchange about the case. The Investigator at the reallocated Study Center will assume the role of the transplant center for the EVLP case and will accept or decline the lungs upon review of the EVLP evaluation data and in consultation with the EVLP Specialist on call.

In the event the host OPO cannot reallocate the lungs to a participating Study Center, the EVLP Specialist will discuss with the host OPO the option of contacting Toronto General Hospital

(TGH) to determine if there is a need at that facility. The decision to reallocate to TGH will rest solely with the host OPO and will be in accordance with their internal policies and procedures. The reallocation will be documented in CMX and on the EVLP facility's CRF. In the event the lungs cannot be reallocated, they will be discarded according to the Sponsor's procedures for handling biomedical waste, or returned to the OPO if requested.

3.2 RATIONALE FOR STUDY DESIGN AND CONTROL GROUP

As described in Section 1, EVLP is a novel technology that allows evaluation of lungs that would not otherwise be used for transplant. This study is designed to show that the CLES is an effective means of enabling a functional evaluation of donor lungs to occur in a controlled, *ex vivo* setting. To achieve this goal, an appropriate subject population must be studied within the unique context of the U.S. organ donation milieu. This presents a number of challenges to a traditional approach to clinical study design that require careful consideration, while not interfering with the life-saving work of the involved OPOs and transplant centers.

This study is a prospective, multi-center, unblinded, non-randomized pivotal study to evaluate the safety and effectiveness of the CLES when used to enable evaluation of donor lungs. This study continues the work done during the feasibility stage of the Sponsor's clinical development under protocol PXUS 14-001 (IDE# G140021), where it was shown to be safe under the conditions of a similar protocol in a similar patient population.

Due to the nature of lung transplantation and EVLP, it is not possible to blind the study centers to the organs that are used in the EVLP treatment group. Study centers are required to refer lungs for EVLP based on an initial evaluation indicating that the lungs would not be used without additional evaluation. Therefore, it is necessary for the Investigator to select lungs specifically for EVLP, then evaluate their function during the EVLP procedure. Additionally, even if a blinded referral process was used whereby the physician referring lungs for EVLP and evaluating their function was not performing the transplant or following the recipient afterward, it is ultimately the responsibility of a transplanting physician to evaluate lung function for their specific patient, and trusting this evaluation to an uninvolved physician would not be acceptable.

Randomization is not possible in this study, as lung transplant is considered a life-saving procedure, so denying a patient a transplant simply because they were not randomized for the available lung is not ethical.

Patients not receiving an EVLP lung who have provided informed consent for participation in this study will be considered for enrollment in a contemporaneous non-EVLP control group. The control group will be selected to best match the EVLP group with respect to the following criteria:

- SLT versus DLT
- LASDDG
- ECMO status at the time of lung allocation

In order to be considered for eligibility, the control patient must “match” *a priori* to an EVLP subject who has already been transplanted. Additionally, to control for variation in surgical and medical practice between study centers, each site is responsible for identifying and enrolling matching controls for the EVLP recipients enrolled at their site.

Data being collected on donors and recipients in the study are by and large a subset of the data typically collected in standard lung transplantation. This familiarity with the data to be collected and collection timepoints is incorporated in the study design to reduce the amount of missing data expected over the course of study completion.

The appropriateness of the primary endpoints is discussed in section [6.12](#) below.

3.3 STUDY DURATION AND DATES

Data will be collected from the organ donor, EVLP procedure (if applicable), and each subject from the time of lung transplantation and up to 12 months post-transplant or until all Serious Adverse Events have been followed as specified elsewhere in this protocol. The study duration (from first patient, first visit [FPFV] to last patient, last visit [LPLV] prior to database lock) is expected to be 36 months.

4 STUDY POPULATION SELECTION

4.1 STUDY POPULATION

The study will be open to all eligible male and female patients, aged 18 years or older, with end-stage lung disease listed for lung transplantation at a participating Study Center.

Study Centers will offer the opportunity to participate in the study to its own patients during time of listing for transplant, during periodically scheduled patient visits or through other means of communication (telephone, mail, etc.). It is expected that enrollment and recruitment activities between male and female recipients will approximate a similar gender mix compared to the Study Center's general lung waitlist.

A sample size of 168 subjects, receiving either SLT or DLT, is planned for this study, where 93 subjects receive donor lung(s) after EVLP (EVLP Group) and 75 subjects are enrolled in a matching contemporaneous control group (Control Group). No less than one-third of the matched subjects enrolled (25 subjects per group) will have received a SLT or DLT. Subjects will be enrolled at up to 16 clinical trial sites (transplant centers).

4.2 INCLUSION CRITERIA

Each patient must meet the following criteria to be enrolled in this study:

1. 18 years of age or older.
2. Male or female
3. Patient actively awaiting a single or double lung transplant.
4. Patient or patient's representative provides informed consent for participation in the study prior to participating in any study-related assessments or procedures.
5. Patient matches with and undergoes a transplant with a donor lung.

4.3 EXCLUSION CRITERIA

Patients who meet any of the following criteria will be excluded from the study:

1. Patients listed for same-side lung re-transplantation.
2. Patients listed for multiple organ transplantation including lung and any other organ.
3. Patients listed for live donor lobar lung transplant.
4. Patients positive for human immunodeficiency virus (HIV) or *Burkholderia cenocepacia* infection.

5. Patient receives a standard of care (non-EVLP) lung transplant but does not match to an EVLP subject based on the criteria for control matching outlined in Section 3.1.
6. Transplanted with a lung that was perfused using another EVLP technology.
7. Participating in another respiratory or cardiovascular clinical trial.

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

This study will be offered to eligible end-stage lung recipients at Study Centers. Recipients will not be compensated for participation, but it is possible that a subject could receive an EVLP--treated lung transplant sooner than they would if they were waiting for a standard lung transplant. EVLP lungs have also been more extensively physiologically assessed than a conventionally procured lung.

Following lung transplant, subjects require routine follow-up visits for immunosuppression monitoring and infection control regimens. For this reason, it is unlikely that subjects will be lost to follow-up unless he/she withdraws consent to participate in the study or changes the healthcare facility where he/she receives follow-up care.

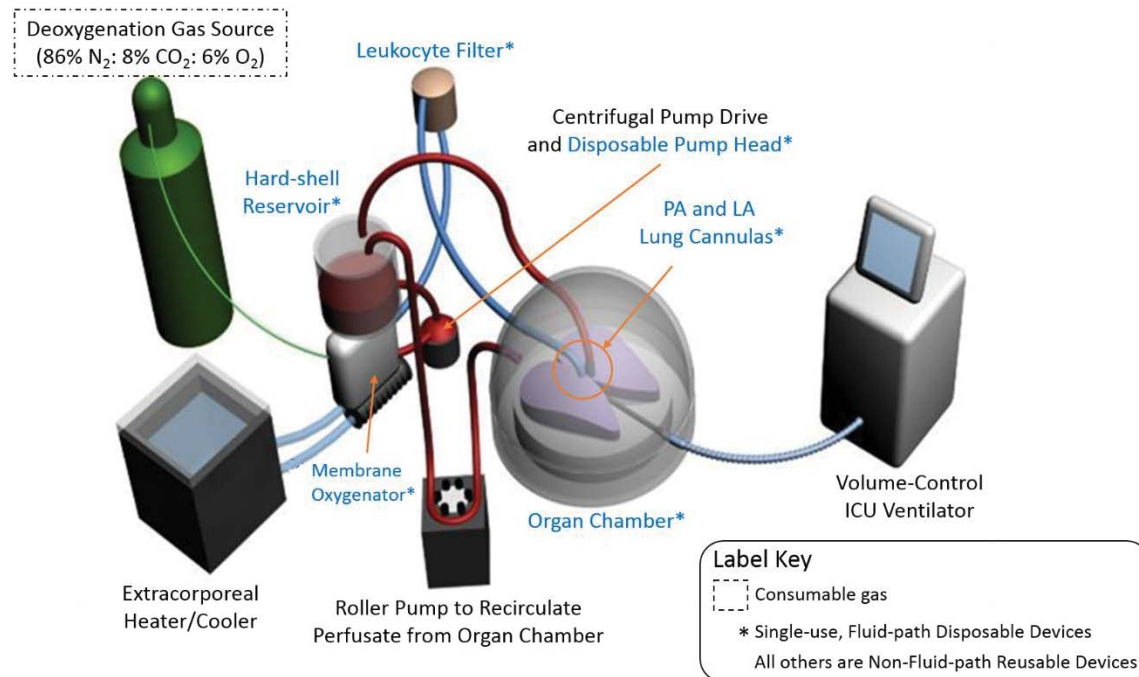
5 STUDY INTERVENTION

5.1 DESCRIPTION OF INTERVENTION

The Sponsor's Ex Vivo Lung Perfusion System ("Centralized Lung Evaluation System" or CLES) comprises a combination of FDA-cleared, off-the-shelf hospital equipment, including: a centrifugal bypass pump, heater/cooler, ICU ventilator, and a disposable bypass perfusion circuit. In addition, the following non-FDA-approved/cleared single-use disposables are necessary: disposable organ chamber, disposable lung cannulas, and the perfusate solution.

There are two classifications of system components: Non-Fluid Path Hardware and Single-Use Fluid Path Disposables. A schematic that represents each classification component in relation to the other is shown in [Figure 2](#).

Figure 2 System Components of the Centralized Lung Evaluation System



The CLES is intended to increase use of deceased donor lungs for transplant by enabling organ evaluation using normothermic perfusion and ventilation in a controlled environment outside the body (*ex vivo*). The device is intended to be used with lungs not otherwise used for transplant into male and female patients aged 18 years or older with end-stage lung disease who are awaiting first time (double or single) lung transplant. The CLES is intended for use exclusively by Lung Bioengineering Inc. in a Company-controlled facility. The CLES is not intended to be operated by any entity that is not a Company-controlled facility. Detailed descriptions of all system components currently in use can be found in the CLES User Manual.

5.2 LUNG EVALUATION DURING EVLP

Donor lungs are not used for standard of care transplantation for any number of reasons. Among those reasons are (but not limited to) the following:

- At the time of the clinical evaluation, the donor $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg;
- Donor received ≥ 10 units of blood transfusions (red blood cell products) as part of their terminal hospitalization;
- Pulmonary edema detected via chest x-ray, bronchoscopy or palpation of lungs;
- Donation after Circulatory Death (DCD) donor;

- Expected cold ischemic time > 6 hrs;
- Donor age $\geq$ 55 years old; or
- Study Center Investigator requires additional evaluation ex vivo in situations when not doing so would result in the lung being discarded.

5.2.1 Donor Lung Inclusion Criteria (Pre-EVLP)

Lungs are eligible for use in this study when an OPO verifies that those lungs would not otherwise be used for transplantation. Participating OPOs will be asked to provide the reason(s) the lungs would not otherwise be used due to one or more of the following:

- Allocation ended: Attempts to place the lungs via the match run sequence have yielded refusal responses to standard (non-EVLP) offers, and the OPO decides that the lack of remaining allocation time supports the decision for EVLP;
- Logistical challenges: The OPO does not have time to perform or complete a lung-specific match run; for example, if the overall organ donation process is being accelerated due to donor deterioration, limited Operating Room (OR) availability, donor family request, procurement teams for other organs with recipient urgency, other competing issues requiring donor surgery to be scheduled prior to lung placement, or allowing another procurement team to recover the lungs for an accepting center;
- DCD: Refusal rates by transplant centers is high in these cases because evaluation of the donor lung function is limited, and donor expiry after withdrawal of care is unpredictable, often not occurring within the time limits established by the transplant centers or donor hospitals. Because of these factors, many transplant centers do not entertain DCD offers at all, meaning that they would not normally be used for transplant;
- OR decline: An unexpected suitability issue is identified at time of procurement resulting in the decision that the previously designated recipient is no longer appropriate; frequently this severely limits the available time for the OPO to reallocate the lungs; or
- Recipient availability: After procurement has started, the original intended recipient is unable to receive the transplant, again, creating a critical timing challenge for the OPO to allocate the lungs to another recipient.
- Other: The OPO may determine the lungs would not otherwise be used for transplant for reasons not listed above. In these cases, additional details will be provided to verify the lungs meet the inclusion criterion.

5.2.2 Donor Lung Exclusion Criteria (Pre-EVLP)

The donor lung is excluded from EVLP if at least one of the following criteria have been met:

- The donor lung has confirmed pneumonia and/or persistent purulent secretions were identified via bronchoscopy prior to donor lung excision;

- Any purulent secretions not considered persistent were identified in the donor lung prior to excision that do not clear by the hour 3 assessment of EVLP;
- The donor lung has confirmed evidence of aspiration;
- The donor lung has significant mechanical lung injury or trauma;
- The donor has HIV or active Hepatitis C; or
- The CIT-1, starting at donor aortic cross clamp/initial flush, required to transport the lung from the donor site to start of the EVLP procedure at a Sponsor facility will be > 10 hrs.

5.2.3 Donor Lung Criteria Post-EVLP Evaluation

Throughout each EVLP procedure, the donor lungs are evaluated for transplant suitability by a Study Center Investigator, in consultation with the EVLP team. The Study Center Investigator will make the final determination of EVLP lung transplant suitability based on the same set of donor lung and recipient risk profiles used to evaluate and accept organs during standard of care donor evaluation.

In addition to the real-time review of the EVLP procedure, the Sponsor will conduct post-EVLP quality reviews of case data to verify compliance with internal policies and procedures.

5.2.3.1 Donor Lung Inclusion Criteria (Post-EVLP)

To be included in this study the donor lung must have completed EVLP and have been accepted by the Study Center Investigator for transplantation. The following criteria will be used to define acceptance by the Study Center Investigator:

- All donor lungs preserved on CLES must meet at least one of the two standard clinical criteria for transplantation at final assessment on the CLES:
 - Final CLES PaO₂/FiO₂ ratio of ≥ 300 mmHg at the end of EVLP; or
 - Stability of pulmonary arterial pressure (PAP), pulmonary vascular resistance (PVR), & peak airway pressure (PAWP) trends defined to be stable or < 20% worsening (i.e. increased) from baseline measurements taken at hour one compared to measurements taken at the end of EVLP.
- AND, the following criterion must be met in addition to the above:
 - Surgeon must be clinically satisfied with the lung evaluation, and if not, the reason for refusal must be listed.
- Any decision to turn down lungs after the lungs have been retrieved, preserved, and assessed on CLES should be done with notification to the Site Principal Investigator and the clinical reason for turning down the donor lung for transplantation shall be documented.

5.3 METHOD OF ASSIGNING PATIENTS TO INTERVENTION

All potential recipients should be approached by his/her treating physician regarding the patient's interest and desire for study information. This may take place during a Screening Visit up to one year prior to transplant, during the Baseline visit on the day of transplant, or at another time prior to transplant. Refer to Section 10.4 for informed consent procedures.

All patients who have provided informed consent to participate in this study will be screened, and eligibility will be assessed according to applicable Inclusion (Section 4.2) and Exclusion Criteria (Section 4.3). Each Study Center will maintain a Screening Log where the applicable patient information will be captured, including their LASDDG, whether he/she is listed for SLT or DLT, and whether they received ECMO during their transplant procedure. Screening logs will be provided to the Sponsor on a regular basis so that patient matching criteria can be tracked. This will allow identification of potential control subjects as EVLP subjects become active in the study upon transplantation.

When lungs are matched from donor to recipient prior to procurement, the Study Center will make the determination if the lung qualifies for EVLP or not (Section 5.2). Based on the outcome of that decision and review of criteria of that lung, either a standard of care transplant takes place or the lung undergoes EVLP to be re-evaluated for possible transplantation.

In situations where the lungs cannot be matched to a recipient due to constraints on the allocation process, an OPO Medical Director can refer the organs for evaluation via EVLP using the Inclusion and Exclusion Criteria listed in Section 5.2 while the allocation process is taking place. Once the allocation is completed, the Study Center with the identified recipient is responsible for evaluating suitability for transplantation and eligibility to be used in the EVLP group based on their clinical judgement and the Inclusion criteria listed in section 5.2.3.1 above.

After at least one EVLP subject has been enrolled at a Study Center, that site's Investigators and team will be notified that a Control Group slot is available for their Study Center, based on the control matching criteria (SLT/ DLT, LASDDG and ECMO status at time of lung allocation). Study Centers will be notified again once that Control Group slot is filled at their site pending the next EVLP transplant. In this way, each Study Center will provide a matching Control Group

subject for each EVLP Group subject enrolled at their site. Control matching must take place as patients are transplanted to maintain a contemporaneously matched group, and to assure that no matching Control group-eligible subjects are missed or skipped. The first eligible, matching, consented transplant recipient at a given Study Center must be enrolled in the Control group in order to eliminate selection bias.

Identification of potential control subjects will be done prospectively. Retrospective matching of control patients after standard lung transplantation is prohibited. Study enrollment commences upon lung transplantation, and enrollment will be tracked separately at each participating center by the Sponsor, using -site-specific identification and coding assigned per the CRF Completion Guidelines. Recipient data provided to the Sponsor will include Subject ID#, but will not include patient-identifying information (name, social security #, etc.). Any consented patient who meets entry criteria, undergoes a standard transplant and is a match for a previously enrolled EVLP patient is considered enrolled in this study, unless that patient withdraws consent in writing. All data obtained prior to withdrawal of consent will be used for this study.

Each participating lung transplant center will maintain a screening and study participant log, recording whether the subject received an EVLP treated or non-EVLP treated lung transplant, as well as SLT or DLT and LASDDG, with subsequent screening identification numbers, dates of informed consent, and transplant dates. For qualifying consented patients that do not enroll into this study, a reason for non-enrollment should be noted to monitor any potential bias.

In order that no less than one-third of the matched subjects enrolled (25 subjects per group) will have received either a SLT or DLT, Study Centers will be kept informed regarding the numbers and types of transplants that have taken place and if any one type of transplant (single or double) will be limited to enrollment to ensure the proportion of either group reaches at least one-third in the overall study.

Furthermore, to ensure the contemporaneous enrollment of Control Group subjects, Study Centers may not enroll more than three EVLP subjects prior to enrolling at least one matching control subject. In this way, at no time should a site have more than three enrolled EVLP

subjects without matched control subjects. The Sponsor will notify any Study Center that reaches this three EVLP patient threshold to remind them that a control patient must be enrolled next.

5.4 BLINDING

This study cannot be blinded to the intervention (standard lung transplant vs. EVLP).

5.5 RESTRICTIONS

There are no protocol-specific restrictions with respect to fluid, food, prior or concurrent medications, or subject activity during this study.

5.6 INTERVENTION AND STUDY PROCEDURE COMPLIANCE

Once a subject receives a lung transplant, he/she is subject to routine follow-up visits due to life-long requirements for immunosuppression monitoring and infection control regimens. For this reason, it is unlikely that subjects will be lost to follow-up unless he/she withdraws consent to participate in the study or changes the healthcare facility where he/she receives follow-up care.

Refer to Section [10.10](#) regarding deviations from the study protocol.

5.7 PACKAGING AND LABELING

Investigational devices will be accompanied by the following label according to 21 Code of Federal Regulations (CFR) § 812.5(a):

“CAUTION-Investigational Device Limited by U.S. Law to Investigational Use”

5.8 STORAGE AND ACCOUNTABILITY

The CLES is comprised of perfusion cart hardware (centrifugal pump, heater/cooler, pressure monitor, ICU ventilator), fluid path and non-fluid path disposables. Additionally, acellular perfusate is used during the EVLP procedure.

All EVLP-related investigational device hardware and disposables will be located and used exclusively at a Sponsor EVLP site. Devices from this study will never be sent to individual transplant study sites. A device disposition log shall be maintained by the Sponsor to track investigational product information including, but not limited to, product lot/serial/batch #, date

of product expiration, manufacturer, date of use, date of disposal of unused product, and the staff initials.

5.8.1 Perfusion Solution

The Sponsor will maintain an inventory log listing the quantity received, lot/batch number, and expiration date. The perfusion solution will be stored in a secure location at the recommended temperature between 4 and 8°C.

Disposal of any opened perfusion solution bottles from each procedure and any leftover solution will be performed according to the Sponsor's standard operating procedures. The solution used during the EVLP procedure contains human serum albumin and may contain some human red blood cells, so it will be disposed of accordingly.

5.8.2 EVLP Disposables

The Sponsor will be responsible for the timely ordering and accurate dispensing of the CLES disposables. The CLES disposables will be shipped and stored at room temperature in a secure location at a Sponsor EVLP site. All disposables will be labeled with the lot number and expiration date and storage and use will be tracked in a validated electronic Inventory Management System. Used disposables are to be discarded in accordance with the Sponsor's policy. No CLES disposables will be shipped from a Sponsor facility to a Study Center.

5.9 INVESTIGATIONAL PRODUCT RETENTION

The Sponsor will be responsible for the accurate storage, inventory, and dispensing of the perfusion solution and the CLES disposables used exclusively at its own site. The CLES disposables include (1) Sterile Organ Chamber, (2) Sterile Lung Cannulas, (3) Sterile Disposable Lung Circuit and (4) perfusion solution.

Required single-use device storage and stability conditions are shown in [Table 1](#).

Table 1 Single-use Device Component Storage and Stability Conditions

Device	Storage Condition	Device Shelf Life
Organ Chamber	Room temperature, store in dry location	4 years
Lung Cannula Set	Room temperature, store in dry location	4 years
Perfusion solution	Store refrigerated between 4-8°C protected from light	2 years
Disposable perfusion circuit	Room temperature, store in dry location	2 years

6 STUDY PROCEDURES

All post-transplant procedures for subjects enrolled in this study will follow the Study Center's standard of care, with additional procedures required as defined below specifically for protocol data collection.

6.1 DONOR AND DONOR LUNG INFORMATION

Data from the donor and donor lung that goes through EVLP will be captured by the EVLP Specialist on a donor/donor lung specific CRF.

During the EVLP procedure, perfusate blood gas samples will be collected by the EVLP Specialist hourly to assess PCO₂, PO₂ and pH both distally and proximally to the lung to assess the lung's capacity to effectively exchange gas.

The Sponsor will collect the following donor information once a donor lung becomes available for EVLP:

- Date of Birth
- Gender
- Ethnicity
- Race
- Weight
- Height
- Date and Time of Death
- Primary Cause of Death
- Mechanism of Death

- Circumstances of Death
- Donor type (Donation after Brain Death or DCD)
- Donor informed consent or next of kin authorization for research
- Hospital information
- PaO₂:FiO₂
- Smoking history
- Chest radiography
- Bronchoscopy findings
- Sputum culture results

For Control Subjects, donor information will not be readily available to the Sponsor; therefore, the donor information listed above must be obtained by the Investigator (or designee) and forwarded to the Sponsor for data entry.

6.2 INFORMED CONSENT

The informed consent process is described in Section [10.4](#).

6.3 MEDICAL HISTORY

Medical history should be obtained by the Study Center for all patients as standard of practice.

Medical history of diseases or conditions ongoing in the year prior to the Screening Visit will be recorded. Medical history will be documented at the Baseline (Day 0) visit, within 24 hrs prior of transplant, to include any updates since the Screening Visit, if a separate Screening Visit occurred. Medical history that is ongoing and began prior to one year before screening should be recorded as “ongoing”. If, in the judgment of the Investigator, there is any medical history one year prior to screening that may be relevant to the patient’s post-transplant outcomes, this should also be recorded.

6.4 CONCOMITANT MEDICATIONS

Concomitant medications should be documented for the 2-week period prior to the onset of an SAE as needed to investigate the event.

6.5 PRIMARY GRAFT DYSFUNCTION SCORE

The subject's PGD Score is to be determined upon admission to the ICU after transplantation, as well as 24, 48, and 72 hrs post-transplant following the 2016 International Society for Heart and Lung Transplantation (ISHLT) PGD definition.[Snell 2017]

PGD Score will be as graded using the parameters in [Table 2](#), where the P/F ratio is $\text{PaO}_2/\text{FiO}_2$.

Table 2 Primary Graft Dysfunction Grading

Grade	P/F Ratio	Pulmonary Edema on Chest X-ray
0	Any	No
1	>300	Yes
2	200 to 300	Yes
3	<200	Yes

Grade severity notes: Patients with no evidence of pulmonary edema on chest X-ray are considered grade 0. Absence of invasive mechanical ventilation should be graded according to the $\text{PaO}_2/\text{FiO}_2$ ratio, using methods similar to those receiving mechanical ventilation. If PaO_2 is not available for calculation of a $\text{PaO}_2/\text{FiO}_2$ ratio, then an oxygen saturation/ FiO_2 ratio should be calculated and the 200 and 300 PGD grading cutoffs should be adjusted to 235 and 315. Use of nitric oxide, aerosolized epoprostenol, or other pharmacologic agents that may improve oxygenation should not change grading methods. Use of extracorporeal life support (ECLS) with bilateral pulmonary edema on chest X-ray image should be graded as grade 3 and ECLS use should be explicitly recorded. The use of ECLS for non-hypoxic indications without pulmonary edema on chest X-ray imaging should be considered un-gradable and explicitly recorded separately.

Time window notes: PGD is graded at 4 time-points over the first 72 hours after transplantation (T0, T24, T48 and T72 hours). T0 is defined as the time of the first blood draw for blood gas testing after admission to the ICU, which should take place within 6 hours of reperfusion of the last lung transplanted. T24, T48 and T72 have time windows ± 6 hours. If multiple blood gas values are available, the worst $\text{PaO}_2/\text{FiO}_2$ ratio in a given assessment period should be used.

Other notes: $\text{PaO}_2/\text{FiO}_2$ should ideally be measured on positive end-expiratory pressure of 5cm H_2O at FiO_2 of 1.0 while patients are on mechanical ventilation; however, grading should not be altered for other settings.

6.6 CHRONIC LUNG ALLOGRAFT DYSFUNCTION

Information on each subject's CLAD status will be collected at Day 90, 6 months and 12 months post-transplant. Sites will be asked to provide information on whether a diagnosis of CLAD has been made on each subject enrolled since their last study visit, and to provide baseline and qualifying Forced Expiratory Volume in one second (FEV_1) and Forced Vital Capacity (FVC) values upon which a diagnosis was made. The CLAD phenotype will be recorded as well as an assessment of relatedness to the allograft received under the study. Finally, if a subject previously diagnosed with CLAD experiences a remission, this information and supporting data will also be collected during a study visit. Reporting CLAD as an adverse event at the time of collecting the information or at the time of diagnosis is not required.

6.7 SURVIVAL

Subject survival, measured as living or dead, will be recorded at Day 30, Day 90, 6 months and 12 months post-transplant, or upon premature termination (if applicable). If the subject expires, the date of death and primary cause of death will be collected. Subsequently, data will be requested for all subjects from the Federal OPTN database for five years post-transplant to document long term survival and safety events. This database enables mandatory data collection for all US transplant recipients as reported by transplant centers. As such, no additional data collection burden is required for participating trial centers or subjects under this protocol.

6.8 CLINICAL LABORATORY TESTS

6.8.1 Laboratory Parameters

During the EVLP procedure, perfusate blood gas samples will be collected by the EVLP Specialist to assess PCO_2 , PaO_2 and pH both distally and proximally to the lung to assess the lung's capacity to effectively exchange gas.

Subject (recipient, post-transplant) arterial blood gases (ABGs) must be determined by the Investigator, in order to calculate PGD grade (Section 6.5), at Baseline (Day 0, within 6 hrs of

admission to the ICU post-transplant), and 24, 48, and 72 hrs thereafter. Laboratory results for tests performed as part of PGD scoring for this study will be recorded on the Primary Graft Dysfunction CRF with the date and time the assessment was performed.

6.8.2 Sample Collection, Storage, and Shipping

The Sponsor will collect pre- and post-EVLP donor lung biopsies for possible future analysis and/or if requested/ required by transplanting center. Additionally, perfusate samples will be collected from the EVLP perfusion circuit for possible future analysis. Samples will be identified by donor ID number. Authorization for collecting and storing donor lung samples pre-transplantation for possible future research purposes will be verified by the Sponsor.

6.9 SAFETY REPORTING

6.9.1 Definitions

Adverse Events

An AE is any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including abnormal laboratory findings) in a clinical investigation subject which does not necessarily have a causal relationship to the investigational medical device. All AEs are assessed by the Study Centers for severity, causality, outcome, seriousness, and if unanticipated, documented as such (see below).

Serious Adverse Event

An SAE is defined by federal regulation as any AE that results in any of the following outcomes: death, life-threatening AE, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unanticipated Adverse Device Effect (UADE)

Any serious adverse device effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Non-reportable Events Non-reportable Events are those that are inherent to the lung transplant surgical procedure and immunosuppressant medications and are expected to occur throughout the postoperative period to be monitored during this study in all subjects.[Lyu 2009] These events do not require reporting and are not considered AEs or SAEs as defined or described elsewhere in this protocol unless the event has a fatal outcome or in the opinion of the investigator could be related to the EVLP procedure, is happening at a higher than expected frequency, or with more than the expected severity. For the purposes of this protocol, Non-reportable Events are listed in [Appendix 2](#).

Events Related to Study Endpoints

Any adverse events that are also defined as study endpoints do not require reporting as AEs since these are reported within the CRF pages specific to study endpoints. For example, PGD within the first 72 hrs does not require separate AE reporting from the Study Center since these events are captured via a specific, dedicated CRF page.

An exception to this is respiratory failure. Respiratory failure must be reported as an Adverse Event and does not have its own CRF page.

Additionally, PGD and CLAD should be reported as AEs or SAEs if the event leads to the death of the subject or if the event is assessed by the investigator as related or possibly related to the device or is unexpected. If these AEs meet UADE criteria, the sponsor will submit them in an expedited manner per current regulatory requirements.

6.9.2 Performing Adverse Events Assessments or Recording of Adverse Events

The Study Center staff will evaluate all potential AEs throughout the study, from the time of transplanted lung reperfusion until the end of the subject's study participation. At all study visits, subjects will be asked about signs or symptoms that may be AEs by a verbal probe (e.g. "How are you feeling?"). Subjects will also be encouraged to contact the Study Center to report such signs or symptoms at any time. Appropriate measures, including medical intervention and/or procedures, will be instituted if clinically indicated at the discretion of the Investigator.

All AEs with the exception of those events discussed in other sections of the protocol that occur during the study must be reported in the CRFs for AEs as described in Section 6.9.7. For each AE, the Investigator will evaluate the severity and seriousness, as well as the relationship of the AE to the device and procedure. Information relating to the AE, such as onset and cessation date and times, seriousness, severity, relationship to device/procedure, action taken, and outcome will also be documented in the subject's source documentation for assessment. Where possible, AEs should be recorded using standard medical terminology. If several signs or symptoms are clearly related to a medically defined diagnosis or syndrome, the diagnosis or syndrome should be recorded, not the individual signs and symptoms.

6.9.3 Timing of Adverse Event Collection

All AEs with the exception of those events discussed in other sections of the protocol are collected and reviewed by the Study Center from the time of transplanted lung reperfusion through the subject's last study visit. Reporting procedures are described in Section 6.9.7.

Subjects with non-serious AEs that are ongoing at the subject's last Study Center visit must be followed until resolution, until they are judged by the Investigator to no longer be clinically significant, or for 30 days after the visit, whichever comes first. All non-serious AEs that are ongoing after follow-up for 30 days' time will be recorded as ongoing. The Investigator is expected to provide or arrange appropriate supportive care for any subject with ongoing AE(s).

Serious adverse events (SAEs) should be followed until they resolve, subject death, subject loss to follow-up or the event or their sequelae stabilize. Supplemental measurements and/or evaluations may be necessary to investigate fully the nature and/or causality of an AE or SAE.

Such supplementary assessments may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. The subject's source documents and CRFs for AEs should be updated with any new or additional information as appropriate.

6.9.4 Severity

The Investigator will use the following scale to grade the severity of any AEs:

- **Mild:** no intervention required; no impact on activities of daily living (ADL)
- **Moderate:** minimal, local, or non-invasive intervention indicated; moderate impact on ADL
- **Severe:** significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

6.9.5 Relationship

The relationship of an AE to EVLP procedure and lung transplant must be assessed by the Investigator using the following guidelines:

- **Related:** The event is associated with the use of the investigational device or with procedures beyond a reasonable doubt
- **Possibly Related:** The relationship with the use of the investigational device or procedure is weak but cannot be ruled out completely; alternative causes are also possible.
- **Unlikely:** The relationship with the use of the investigational device or procedure seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- **Not related:** There is no temporal relationship between the investigational device or procedure and the event onset, an alternate etiology has been established.

6.9.6 Expectedness

The Sponsor and the Study Principal Investigator will be responsible for determining whether an SAE is expected or unexpected. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the EVLP device (See [Appendix 5](#)), and/or if the observed event is atypical given a specific patient's clinical history or a specific site's clinical experience. Events defined in [Appendix 2](#) do not require reporting as serious or non-serious adverse events for either the Control Group or the EVLP Group unless the event has a fatal outcome, or in the opinion of the investigator could be

related to the EVLP procedure, is happening at a higher than expected frequency, or with more than the expected severity.

6.9.7 Reporting Procedures

Study Centers will report to the Sponsor all non-serious AEs (with the exception of Non-reportable Events expected in lung transplant recipients as noted in [Appendix 2](#)) from transplanted organ reperfusion through 90 days post-transplant, and all SAEs while a subject is enrolled in the study, until their last study visit. The Sponsor will report all non-serious AEs occurring during the first 90 days post-transplant, and all SAEs while a subject is enrolled in the study to the FDA in the annual Investigational Device Exemption (IDE) report. Each reported AE will include date of onset, actions taken, severity, seriousness of the event, relationship of the event to the EVLP procedure and lung transplant, and the outcome of the event.

6.9.7.1 Reporting Serious Adverse Events

All SAEs shall be reported to the Sponsor within 24 hours after awareness via the Adverse Event CRF. The Sponsor shall review all SAEs to assess if related or anticipated/expected. Any event that meets the serious criteria, is unanticipated/unexpected per Sponsor assessment, and assessed by the Sponsor as related to the device system is subject to expedited reporting to FDA and participating IRBs in accordance with the Unanticipated Adverse Device Effect requirements (21 CFR 812.150). The Sponsor or Sponsor's representative will report any results of an evaluation of UADE to the FDA, the Central Institutional Review Board (IRB), and all Investigators within 10 business days following receipt of notice of the event(s).

All other SAEs will be reported to FDA in the annual IDE report.

In addition to the above, it is the responsibility of the Study Investigator to abide by the AE reporting requirements stipulated by local IRBs.

6.9.7.2 Reporting Procedure for Serious Adverse Events

Any AE meeting the specified SAE criteria will be recorded on an AE CRF in the Electronic Data Capture (EDC) for direct transmission to the Safety database. In instances that the site is unable to enter the SAE electronically directly into EDC system, the alternative for reporting is reporting on the paper SAE Report Form which should be sent to United Therapeutics

Corporation Global Product Safety/Pharmacovigilance by email or fax if the EDC is not available. Once a paper SAE form is submitted, an automatic acknowledgement will be returned to the reporter by email. The Investigator or the site staff should contact United Therapeutics Corporation Global Product Safety/Pharmacovigilance if this confirmation is not received. This process applies to both initial and follow-up SAE reports.

SAE Reporting Contact Information:

Email: drugsafety@unither.com
Back-up fax line (US): 919-313-1297

If a paper SAE form is submitted, the site will be required to enter the data in the EDC system as soon as they are able to do so.

General questions about SAE reporting can be directed to the Safety Help Email:
GDS_LBE301@unither.com.

The Investigator must also promptly notify their local IRB of the SAE, including any follow-up information, in accordance with applicable national regulations and guidelines set forth by the IRB.

6.9.8 Halting Rules

The sponsor shall suspend enrollment if there are any of the following in the ELVP group:

- Three subject deaths within the first 30 days post-transplant; or
- PGD3 rate at T72 hours for lungs (both double and single, combined) $\geq 35\%$ after enrollment of at least 10 subjects; or
- A determination by the DMC of unacceptable risk to subjects based on review of study data. Enrollment will be suspended until the DMC can review study data and render an analysis, and mitigating steps can be established by the sponsor (if appropriate) and accepted by the DMC, each IRB and FDA.

Refer to section [6.5](#) above for PGD scoring in accordance with ISHLT 2016 Guidelines. [Snell 2017]

6.10 REMOVAL OF SUBJECTS FROM THE STUDY

Subjects may withdraw voluntarily from the study or the Investigator may terminate a subject's participation. Withdrawing from the study will not affect subject's status/ability to receive a standard lung transplant.

Subjects are free to withdraw from participation in the study at any time upon request.

The Investigator may withdraw a subject from the study for any reason, including but not limited to, the following:

- Any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject;
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation;
- A protocol deviation occurs; or
- The Sponsor or Investigator terminates the study.

It is unlikely that a subject will discontinue study participation after receiving a lung transplant, as a lifetime of required follow-up, immunosuppression monitoring, and infection control is required after transplantation to minimize the chance of graft failure and/or death. Every effort will be made to undertake protocol-specified safety follow-up procedures to capture AEs, SAEs, and UADEs.

6.11 PREMATURE TERMINATION OR SUSPENSION OF THE STUDY

This study may be suspended or prematurely terminated with Agency concurrence if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Study Investigators, the IDE Sponsor, and all regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects;

- Insufficient adherence to protocol requirements;
- Data that are not sufficiently complete and/or evaluable;
- Determination of futility; or
- Determination that evidence collected to date clearly demonstrates that EVLP is safe and effective for transplantation of lungs that would not otherwise be used.

6.12 APPROPRIATENESS OF MEASUREMENTS

Twelve-month survival is the primary endpoint measured for subjects in this study (Section 2.1).

The endpoint is a comparison of mortality at the later of 12 months or first hospital discharge post-transplant, compared to a performance goal derived from historical outcome data of standard of care transplant recipients. The performance goal is derived from the combined incidence of waitlist mortality, waitlist removal for clinical worsening, and post-transplant mortality rates for the most recent datasets published by the Scientific Registry of Transplant Recipients (SRTR) under contract with the United States Department of Health and Human Services. [SRTR, 2020]

For the most recent data cohort reported (patients listed between 01 July 2017 and 30 June 2018), 9.3% of candidates either died awaiting transplant or were removed from the waitlist for clinical worsening within 12 months of being listed.

For the most recent data cohort reported (transplants performed between 01 January 2017 and 30 June 2019) the estimated probability of survival after receiving a lung transplant at 12 months was 89.46%. This equates to an estimated probability of mortality within 12 months post-transplant of 10.54%. Therefore, the combined waitlist mortality, removal due to clinical worsening and post-transplant survival at 12 months is 19.84% equating to a 12 month overall survival of 80.16%.

Given that EVLP is intended to increase the number of lungs available for transplant, it is necessary to include this as a measure of device effectiveness as a comparison to the number of patients that may die or deteriorate to the point of removal from the waitlist while waiting for a lung transplant that never happened. Additionally, post-transplant survival is an important measure of safety, so consideration for EVLP recipient survival as an outcome is included in the

Performance Goal. The Performance Goal of $\geq 81.2\%$ survival ensures the cited combined survival of 80.16% is met.

The primary endpoint is evaluated at 12 months post-transplant (or at first hospital discharge, whichever is later) rather than at longer intervals for several reasons. First, confounding recipient characteristics resulting from the relatively small number of lung transplants make true matching between the study cohort and any contemporaneous control group extremely challenging. Because these various factors may have increasing influence on overall clinical outcome, a shorter evaluation window minimizes the bias introduced by these unmatched confounders. Second, EVLP is a pre-transplant procedure, and negative device associated events resulting from EVLP will almost certainly be identified during the early post-transplant time frame. The Sponsor recognizes that longer term outcomes after lung transplant remain important and relevant, and therefore proposes to continue following enrolled subjects up to 5 years post-transplant under a separate data collection method described above. In addition to this protocol, a follow up registry of all study subjects plus future patients who receive lung transplants after EVLP at a Lung Bioengineering facility will be implemented to explore outcomes both in a real world setting and in the 5 year post-transplant period.

7 STUDY ACTIVITIES

A review of the transplant candidate files, donor information, and lung evaluation is required to determine preliminary eligibility according to recipient and donor lung inclusion and exclusion criteria.

Unless otherwise indicated herein, all activities will be conducted and data collected for both control and EVLP subjects.

The Study Schedule of Events is tabulated in [Appendix 1](#).

7.1 SCREENING VISIT (DAYS -365 TO -1 [-24 HOURS])

A Screening Visit may occur any time from up to one year to the day of lung transplant. The following may be conducted during this visit:

- Obtain informed consent per Section [10.4](#);

- Determine patient eligibility according to applicable Inclusion (Section 4.2) and Exclusion Criteria (Section 4.3).
- Collect demographics, such as date of birth, age, gender, ethnicity, race, weight and height; and
- Document Medical History of diseases or conditions ongoing in the past year per Section 6.3.

7.2 INTERVENTION

7.2.1 Lung Assessment, Lung Transplant, and Baseline (Day 0)

7.2.1.1 Donor Lung Screening (Day 0, within 24 hours prior to transplant)

For EVLP lung donors, the Sponsor will perform the following:

- Collect donor information (see Section 6.1); and
- Confirm donor lung eligibility according to the donor Inclusion (Section 5.2.1) and Exclusion criteria (Section 5.2.2) for EVLP evaluation.

For Control subjects, the Investigator will perform the following:

- Collect donor information (see Section 6.1); and
- Forward donor information for entry into Sponsor CRF

7.2.1.2 Recipient Screening (Day 0, within 24 hours before transplant)

For both EVLP and Control subjects, the Investigator will perform the following:

- Obtain Informed Consent (if not previously done) in accordance with the IRB policy;
- Document a conversation in the patient's record in which their continued willingness to participate in the study is confirmed if they have previously provided Informed Consent;
- Collect and/or update the following recipient information if not previously collected:
 - Medical history
 - Date of Birth
 - Gender
 - Ethnicity
 - Race
 - Weight
 - Height
 - LASDDG
 - Lung Allocation Score (LAS)

- Oxygen requirements at rest (L/min)
- Perform physical examination; and
- Confirm recipient eligibility in accordance with the recipient Inclusion (Section 4.2) and Exclusion Criteria (Section 4.3).

7.2.1.3 Donor Lung EVLP Evaluation (at completion)

The Sponsor will perform the following:

- Record preservation information including cross clamp time/ start of first cold preservation (CIT-1);
- Collect lung function data to be used as part of the EVLP suitability evaluation that is performed by the Study Center Investigator.
- Confirm donor lung eligibility in accordance with the donor lung Inclusion (Section 5.2.3.1) for transplant suitability after EVLP; and
- Preserve, package and ship the organs to the accepting Study Center.

7.2.1.4 Lung Transplantation and Baseline (Day 0)

Provided all recipient and lung Inclusion and Exclusion Criteria have been met, the Investigator or his/her designee will record or perform the following after admission to the ICU, within 6 hours of last lung reperfusion:

- Hospital admission date;
- Transplant date and time, including first stitch in the anastomosis time for each lung;
- ICU admission time and date;
- Initial PaO₂, FiO₂ and O₂ saturation; values and time collected (Baseline);
- Chest radiograph; and
- Assess AEs.

7.3 POST-INTERVENTION PERIOD (DAY 1 TO 30 DAYS/FIRST HOSPITAL DISCHARGE POST-TRANSPLANT)

7.3.1 Visit 1 Procedures (24 Hours post-Baseline)

At 24 hrs post-Baseline ($\pm$ 6 hrs), the Investigator or his/her designee should record or perform the following:

- PaO₂, FiO₂ and O₂ saturation;
- Chest radiograph; and
- Assess AEs.

7.3.2 Visit 2 Procedures (48 Hours post-Baseline)

At 48 hrs post-Baseline ($\pm$ 6 hrs), the Investigator or his/her designee should record or perform the following:

- PaO₂, FiO₂ and O₂ saturation;
- Chest radiograph; and
- Assess AEs.

7.3.3 Visit 3 Procedures (72 Hours post-Baseline)

At 72 hrs post-Baseline ($\pm$ 6 hrs), the Investigator or his/her designee should record or perform the following:

- PaO₂, FiO₂ and O₂ saturation;
- Chest radiograph;
- Record extubation date/time (if applicable);
- Record ICU discharge time/date (if applicable); and
- Assess AEs.

7.3.4 Visit 4 Procedures (Day 30 post-transplant)

On Day 30 ($\pm$ 5 days) post-transplant, the Investigator or his/her designee should record the following:

- Subject survival;
- If extubated >72 hrs post-transplant, extubation date and time (if applicable);
- Oxygen required at rest at time of hospital discharge (if applicable and not previously recorded);
- ICU discharge date and time (if applicable and not previously recorded);
- Hospital discharge date and readmission date(s) (if applicable); and
- Assess AEs.

7.3.5 Visit 5 (Day 90 post-transplant)

On Day 90 post-transplant ($\pm$ 10 days), the Investigator or his/her designee should record the following:

- Subject survival;
- CLAD Status;

- FEV₁;
- Oxygen required at rest;
- Physical capacity;
- Working for income status;
- ICU discharge date and time (if applicable and not previously recorded);
- Hospital discharge date (if not previously recorded) and readmission date(s) (if applicable); and
- Assess AEs.

7.3.6 Visit 6 (Month 6 post-transplant/First Hospital Discharge post-transplant)

At 6 months ($\pm$ 14 days) post-transplant, the Investigator or his/her designee should record the following:

- Subject survival;
- CLAD Status;
- FEV₁;
- Oxygen required at rest;
- Physical capacity;
- Working for income status;
- ICU discharge date and time (if applicable and not previously recorded);
- Hospital discharge date (if not previously recorded) and readmission date(s) (if applicable); and
- Assess AEs.

7.3.7 Visit 7 / Final Visit (12 months post-transplant)

At 12 months ($\pm$ 30 days) post-transplant, or date of first hospital discharge, if later, the Investigator or his/her designee should record the following:

- Subject survival;
- CLAD Status;
- FEV₁;
- Oxygen required at rest;
- Physical capacity;
- Working for income status;
- ICU discharge date and time (if applicable and not previously recorded);

- Hospital discharge date (if not previously recorded) and readmission date(s) (if applicable); and
- Assess AEs.

7.4 EARLY TERMINATION PROCEDURES

As lung transplant requires life-long follow-up care from the transplant center, it is unlikely a subject will withdraw from this study post-transplant. Subjects may withdraw consent to participate prior to receiving the intervention (lung transplant) within this study without consequence to the subject or study. In the event that a patient withdraws consent after lung transplant, the following data will be collected by the Study Center either through OPTN and/or SRTR reports or via an early termination visit:

- Subject survival;
- CLAD Status (if after Visit 5);
- FEV₁ (if after Visit 4);
- Oxygen required at rest;
- ICU discharge date and time (if applicable and not previously recorded);
- Hospital discharge date (if not previously recorded) and readmission date(s) (if applicable);
- Physical Capacity;
- Working for Income status; and
- Assess AEs/SAEs.

7.5 UNSCHEDULED VISITS

Upon receiving any lung transplant, a subject may require a number of unscheduled visits for a variety of reasons, including infection and rejection. If an unscheduled visit is performed due to a documentable AE, then it will be tracked as such.

8 QUALITY CONTROL AND ASSURANCE

The sponsor is responsible for ensuring that the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements. To this end, the clinical monitor will make periodic study site visits to assess compliance with the protocol, verify the data collected, and identify and resolve problems that may arise. The investigator agrees to allow the monitor direct

access to all relevant study documents and to allocate time to discuss findings and any relevant issues.

The sponsor may conduct a quality assurance audit of this study. If such an audit occurs, the investigator agrees to allow the auditor direct access to all relevant study documents and to allocate time to discuss findings and any relevant issues. In addition, this study is subject to audit by the relevant Regulatory Authorities. If such a regulatory inspection occurs, the investigator agrees to allow the inspector direct access to all relevant study documents.

The Sponsor will conduct the EVLP procedure exclusively at the Sponsor's dedicated facility. All post-EVLP procedures will be reviewed by an in-house Quality Assurance (QA) manager for compliance with the CLES User Manual and clinical trial protocol, as well as for accuracy in relation to source documents. In addition, the Sponsor will use an independent Contract Research Organization (CRO) to oversee specifically delegated activities. Finally, an independent CEC will review all adverse event and mortality data to assess the relationship to the EVLP procedure and lung transplantation(Section [10.9](#)).

8.1 TRAINING FOR STUDY INVESTIGATORS

Training will be completed prior to participation in the clinical trial as outlined in the following sections.

8.1.1 Transplant Center Research Personnel

Study Center site personnel will be trained on study activities, obtaining informed consent, and the study protocol, and will be provided a review of Good Clinical Practice (GCP) if not previously provided by the institution. Human Subjects Protection training shall be provided by each participating institution.

8.1.2 EVLP Specialists

All EVLP Specialists performing procedures at a Sponsor facility will have extensive training in the Toronto EVLP Method through a trainee in-residence program at TGH. Details of this training program can be found in [Appendix 3](#).

9 PLANNED STATISTICAL METHODS

9.1 GENERAL CONSIDERATIONS

This section describes the planned statistical analyses in general terms. A complete description of the methodology will be specified in a statistical analysis plan (SAP), which will be finalized prior to enrollment of the first patient in the study. Any changes in the statistical methods described in this protocol after the start of the study will be submitted to FDA for review via an IDE Supplement.

The database will be locked for analysis of endpoints after the last subject completes his/her last Study Center visit and all on-going AEs have been followed as required per this protocol, whichever is later, and all queries have been resolved.

For ease of presentation, contextual review and statistical programming, the descriptive statistics of the contemporaneous Control group will be presented with those of the EVLP group. Descriptive statistics will be presented as means, standard deviations (SD), medians, and ranges for the continuous variables and as frequencies and percentages for categorical variables. Tabulations will be used to summarize results from descriptive summaries and statistical analyses. Two-sided 95.0% CIs will be provided for the primary and secondary endpoints, as appropriate to the data.

9.2 DETERMINATION OF SAMPLE SIZE

9.2.1 12 Month Mortality

Sample size for this device trial is determined by the Bayesian approach with power prior (Ibrahim and Chen 2000, Pennello and Thompson 2008). In order to provide a sufficient number of subjects to support a formal statistical comparison of the primary endpoint of 12 month survival rate to the performance goal, sample size was calculated based on an expected 12 month survival rate of 89.2% (Valapour, 2018). Given two sets of historical 12 month survival data from the feasibility study (section 1.1.2) and recent Toronto EVLP data during year 2016 to year 2018 (section 1.1.1), a sample size of 93 subjects would provide at least 80% power at a significance level of 0.1, to confirm that the posterior probability of 12 month survival rate greater than the performance goal of 81.2% (with a margin=0.08; see rationale Section 6.12) is greater than 0.95 (see [Appendix 4](#) for a more detailed discussion).

As EVLP transplants may be either transplant subtype (single-lung or double-lung) and reliable estimation for potential subgroup analyses of the primary endpoint in each transplant subtype is desired, the overall sample size of 168 subjects will include a minimum of 75 matched subjects in each group for the study, and enrollment to either transplant subtype within each group will be at least 25 subjects by specified design. In this way, there will be 25 EVLP DLT recipients matched to 25 DLT Control recipients, and 25 EVLP SLT recipients matched to 25 Control SLT recipients.

A complete description of the Bayesian methodology and data simulation is specified in Appendix 4. Detailed analysis methods will be specified in a statistical analysis plan (SAP), which will be finalized prior to the final EVLP transplant in the study. Any changes in the statistical methods described in this protocol will be documented in the statistical analysis plan.

9.2.2 Control Group

A contemporaneous Control group will be entered into this study. This Control group will provide context of the EVLP results and estimation of Control group parameters for design of future studies. All analyses of the Control group will be descriptive, and no formal statistical comparison will be made between the EVLP and Control groups. As such, the sample size for the Control group will be at least 75 subjects, and subjects will be matched to the EVLP Group for similarity. The Sponsor retains the ability to enroll up to a maximum of 93 in each group but will end enrollment once 75 matched Control cases are enrolled. For this reason, it is possible that EVLP group enrollment will reach the maximum (93) before the Control group reaches the minimum (75).

9.3 ANALYSIS POPULATIONS

Two analysis populations will be considered for this study:

- **Full Analysis Set:** Includes all subjects in the EVLP group regardless of subject outcome or subsequent re-transplant. Analyses will include all subjects in the EVLP group. This population will be used for the primary and secondary endpoint and safety analyses.
- **Ancillary population:** Includes all subjects who have received either a transplant by EVLP or standard of care (matching required per Section 5.3). This population will be used for a supportive safety analysis.

All subjects will be included in the analyses to the extent data are available. Planned exceptions will be noted in the SAP.

Deviations from inclusion/exclusion criteria will be listed by subject.

9.4 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic data and baseline characteristics for all subjects collected prior to transplant will be listed and summarized overall, by Transplant Group (EVLP or Control), as well as by transplant subtype (SLT or DLT) using descriptive statistics.

Medical history (medical conditions ending prior to EVLP transplant) will be coded using the WHO-drug dictionary, presented as a listing and summarized overall and by transplant subtype using the system organ class (SOC).

9.5 PRIMARY ENDPOINT

9.5.1 12 Month Mortality

Post-transplant survival measured as the combined incidence of 12 month mortality and mortality prior to first hospital discharge after the lung transplant procedure.

Subject survival, measured as living or dead, will be recorded at the later of 12 months or first hospital discharge post-transplant. The primary endpoint will be derived as follows: Living at 12 months /Day of Discharge will be coded to 1, and Dead before or on 12 months /Day of Discharge will be coded to 0. If the vital status of the subject is missing (not collected, not reported, not properly documented), then 12 month vital status will be imputed as Dead for the primary analysis. A sensitivity analysis to impute 12 month vital status to be alive for subjects with missing vital status will also be done.

The primary analysis will be to calculate the posterior probability of the 12 month survival rate greater than the performance goal of 81.2%, the primary objective will be achieved if the posterior probability is greater than 0.95. The proportion of subjects with 12 month survival will be summarized by Transplant Group. A two-sided 95% CI of the 12 month survival rate will be calculated. The 12 month survival rate will also be compared between the treatment group and the contemporaneous control group.

Other supportive endpoints may be provided to supplement the primary analysis, including, but not limited to, median number of days to death and primary cause of death.

Results may be displayed graphically.

9.6 SECONDARY ENDPOINTS

The secondary endpoints will be presented using descriptive statistics along with two sided 95% CIs. Other supportive endpoints may be provided to supplement the secondary analyses.

Results may be displayed graphically. There will be no inferential testing conducted. The Secondary Endpoints are:

- Adjudicated lung graft-related mortality measured as the percentage of study subject deaths determined to be related directly or indirectly to the transplanted organ
- Utilization rate of EVLP lungs measured as the number of EVLP procedures resulting in lungs accepted for transplant divided by the number of EVLP procedures performed on lungs referred for EVLP.
- Increase in use of donor lungs measured by the number of lungs referred for EVLP and accepted for transplantation at a Study Center without the use of EVLP;
- Subject survival at 30 days post-transplant;
- Subject survival at 90 days post-transplant;
- Subject survival at 6 months post-transplant;
- Subject survival at 12 months post-transplant;
- PGD Score (Grades 0-3) measured at 0, 24, 48 and 72 hours post-transplant;
- Duration of subject ventilator support, measured as total number of hours post-transplant ventilator support is required prior to initial hospital discharge;
- Rate of ECMO use post-transplant measured as the proportion of subjects that require ECMO support for any reason and at any time prior to initial hospital discharge after transplantation;
- Intensive care unit (ICU) length of stay (LOS), measured as total number of days post-transplant in the ICU until first hospital discharge, inclusive of ICU readmissions during the initial transplant hospitalization;
- Hospital LOS measured as total number of days in the hospital until first discharge post-transplant;
- Extended evaluation and preservation time, defined as the elapsed time between donor aortic cross clamp at procurement and placement of the first stitch in the anastomosis at transplant. This time is recorded separately for each lung transplanted in a double lung procedure;

- Assessment of the overall safety of CLES lung transplants during each subject's participation in the study, as reported through adverse events (AEs);
- Rate of Chronic Lung Allograft Dysfunction (CLAD) measured as number of subjects diagnosed with CLAD post-transplant;
- Rate of respiratory failure; and
- FEV₁ values at defined timepoints

In addition, supplemental analyses comparing the EVLP group and the Control Group may be performed to provide context of results observed in this study (details will be described in the SAP).

Primary and secondary endpoints will also be presented for evaluation of outcomes for the following subgroups within the EVLP and control groups:

- center enrollment numbers;
- single- or double-lung transplantation;
- cold ischemia time (first lung and second lung);
- total preservation time (first lung and second lung);
- donor lung criteria (standard vs expanded);
- donor lung source (OPO vs transplant center referral) and
- use of pre-operative recipient ECMO (use vs. non-use).

The sponsor may add additional subgroup assessments or modify presentation of the above based on data collected, e.g., cases where small numbers prevent informative analysis, e.g., <5 cases, results may be suppressed, quartiles presented instead of median split, etc. Any such modifications to the above and reasons for modifications will be documented in the study report.

Standard criteria donor lungs are defined as those meeting the minimum characteristics per the ISHLT 2020 Consensus Statement. [Copeland, 2020]

9.7 MISSING DATA

The primary endpoint is the proportion of subjects who die prior to 12 months or first hospital discharge post-transplant if later.

If the mortality value is missing (not collected, not reported, not properly documented), then it will be classified as a “death” for the primary safety analysis.

9.8 OTHER SAFETY ASSESSMENTS

9.8.1 Adverse Events

Study Centers will report to the Sponsor all AEs from transplanted organ reperfusion through 90 days post-transplant, and all SAEs until the subjects’ last study visit. Adverse events and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Intervention-emergent AEs will be defined as those events, which are newly occurring or worsening from Baseline (Day 0). In all cases only intervention-emergent AEs will be summarized.

Intervention-emergent AEs will be summarized by Transplant Group as the number and percentage of subjects having any intervention-emergent AE, having an AE in each body system, and having each individual AE. Adverse events will further be categorized by severity, relationship to study intervention, and action taken. Other information collected will be listed, as appropriate.

9.8.2 Pregnancy Reports

If a study subject becomes pregnant during participation in this clinical study, a Pregnancy Notification and Outcome Form should be completed by the investigator/site, and the report will be sent to United Therapeutics Corporation Global Product Safety/Pharmacovigilance by e-mail via DrugSafety@unither.com (primary method) or fax to +1 919-313-1297 (back-up method) within 1 working day of awareness. The outcome of the pregnancy will also be reported on the Pregnancy Notification and Outcome Form within 1 working day of awareness. For live births, the One Year Infant Follow up Form should be provided.

The designated vendor case processor will enter the information from the pregnancy report into the global safety database and perform any needed follow-up.

Abnormal outcomes of a pregnancy for mother or child should be reported as an AE or an SAE. Spontaneous abortions, termination for medical reasons other than underlying disease, pre-term

delivery, ectopic pregnancy, or a congenital anomaly in the offspring should all be reported as SAEs.

9.9 INTERIM ANALYSIS

There are no formal interim analyses planned for this study.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The term “Investigator” as used in this protocol and in the CRFs refers to the Principal Investigator at each study site, or another staff member listed as a sub-investigator on the study site delegation log. The site Principal Investigator is ultimately responsible for the conduct of all aspects of the study at that site. The site Principal Investigator is also responsible for ensuring that all site staff working on the study are appropriately trained and supervised; staff training and delegation of responsibilities should be documented in the files.

Prior to site activation, the Investigator must read, understand, and sign the Investigator Agreement in the protocol. The Investigator Agreement documents agreement to conduct the study according to the protocol, International Council for Harmonisation / Good Clinical Practice (ICH/GCP), and Code of Federal Regulations (CFR). Additional requirements must be met by the Investigator and institution, as described below.

10.2 INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to each participating study site’s local IRB for review and approval. In addition, the Sponsor will operate its EVLP site under the review of an independent third-party IRB.

Approval of both the protocol and the ICF must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

Each IRB must operate in compliance with 21 CFR Part 56, including being registered with the FDA. The IRB is to provide some form of documentation of compliance via a Statement of Compliance and/or a Federal Wide Assurance Number. If any member of the research team is a

member of the IRB, written documentation is required that he/she did not vote or participate in the approval process

10.3 ETHICAL CONDUCT OF THE STUDY

The Investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

10.4 AUTHORIZATION AND CONSENT

10.4.1 Donor Next of Kin Authorization

Authorization for organ donation will be obtained by the federally-designated OPO in accordance with the requirements of the Uniform Anatomical Gift Act in the state of the donor hospital and in compliance with OPTN Policy 2.[OPTN 2020] The OPO also must comply with its internal policy regarding donor (or donor family) authorization for additional lung evaluation using EVLP, and for the use of donor information and biopsy samples for research.

10.4.2 Subject (Recipient) Consent

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Subjects listed or being considered for listing for single or double lung transplantation with UNOS may be offered the option to participate in this study.

A Legally Authorized Representative may be used to consent for a subject that is unable to communicate or understand the information being presented to them. The potential subject's condition should be considered, and a determination made that participating in the study is consistent with any previously expressed wishes (e.g. Advanced Directive, Living Will, witnessed conversation), is in their best interest and whether other available medical options, including waiting for the next available non-study organ, are unavailable or may not be available in time to prevent disease progression and death. The Study Center must adhere to IRB and State law requirements as to who is an acceptable Legally Authorized Representative. The Study

Center will also obtain documentation that the person signing consent is authorized to do so. If at any time after the Legally Authorized Representative provides consent, the subject or potential subject regains the ability to communicate and understand the information presented during the consent process then they will be asked to execute a new Informed Consent Form.

Extensive discussion of risks and possible benefits of study participation will be provided to subjects or Legally Authorized Representative and their families. A consent form describing in detail the study procedures and risks will be provided to document the decision. Each participating Study Center will be provided with a model ICF. Each institution may revise or add information to comply with institution consent templates but may not remove procedural or risk content from the model form. Consent forms will be IRB-approved, and the subject or Legally Authorized Representative is required to read and review the document or have the document read to him or her. The Investigator or designee will explain the research study and answer any questions that may arise.

The subject or Legally Authorized Representative will sign the ICF prior to any study-related assessments or procedures. Study related assessments are defined as any study activities in which data are specifically collected from a potential subject that could later be used for analysis under this protocol. Prescreening of potential subjects based on previously known medical histories or other information is not considered a study related assessment. Study related procedures are any medical procedures performed to screen or prepare a subject for lung transplantation under this protocol. Screening or other procedures performed for the purposes of general lung transplantation suitability or compatibility are not considered study related procedures.

If consent is obtained the same day that the subject begins study-related assessments or procedures, the subject's medical record should document that consent was obtained prior to these activities. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The consent may be signed during an extended period of time prior to the transplant. This extended period timeframe shall be determined by the local IRB in reference to the timeframe before a subject is re-consenting versus reaffirming the original consent. The consent obtained prior to the day of transplant shall be confirmed at day of transplant by subject or subject's Legally Authorized Representative. This shall be documented

in the source document by the site staff and will not involve the resigning of the consent unless requested by the IRB. A subject or their Legally Authorized Representative may withdraw consent at any time throughout the course of the study.

A copy of the signed ICF will be given to subjects or Legally Authorized Representatives for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

A subject is only considered enrolled in the study when he/she or their Legally Authorized Representative has signed the ICF and, at an approved Study Center, is transplanted with a donor lung.

10.5 SUBJECT CONFIDENTIALITY

Subject confidentiality is strictly held in trust by the Investigators, study staff, and the Sponsor and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to subjects. Donor records will be redacted for any identifying donor information and instead will only use a pre-assigned UNOS Donor ID# to connect donor to recipient. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The Investigator/Institution will permit direct access to source data and documents by Sponsor, its designee, the FDA, and other applicable regulatory authorities. The access may consist of study-related monitoring, audits, IRB/Independent Ethics Committee reviews, and FDA/regulatory authority inspections.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

10.6 STUDY MONITORING

The study will be monitored according to a formal Monitoring Plan, and as summarized below. Both centralized and onsite monitoring will be performed for this study. The Sponsor may choose to perform random inspections throughout the study as an element of quality assurance. Investigators shall allow auditing of their clinical investigation procedures and data.

Data will be collected from EVLP lung transplant recipients and the non-EVLP lung transplant recipients included in the Control Cohort. These data will include basic lung transplant information along with primary and secondary endpoints as listed in this protocol.

The monitor(s) will visit the site soon after the first subject is enrolled to assist in any questions the site might have concerning the study or CRF completion. Monitoring visits will occur based on number of subjects enrolled at a Study Center, duration of the study, level of compliance or a significant change in compliance, or a change in Study Center staff.

It is the responsibility of the study Sponsor to ensure that proper monitoring of this investigation is conducted. Appropriately trained personnel, appointed by the Sponsor, will complete any monitoring that is performed. The monitoring will be the responsibility of Sponsor study personnel or as designated. Monitors will ensure that the investigation is conducted in accordance with:

- The signed Investigator's Agreement;
- The study protocol;
- Appropriate laws and regulations; and
- Any approval conditions imposed by reviewing IRB and/or regulatory agencies.

10.6.1 Access to Centers

The Investigator is required to permit monitoring and study record access in order for the monitors to perform their responsibility. The Investigator(s), co-investigator(s), and other study staff must be available during site visits by the study monitor. The Sponsor may choose to perform random inspections throughout the study as an element of QA. Investigators shall allow auditing of their clinical investigation procedures.

10.6.2 Summary of Monitoring Procedures & Responsibilities

It is the responsibility of the study Sponsor to ensure that proper monitoring of the investigations is conducted and that IRB review and approval of the investigation is obtained. Monitoring visits will occur based on number of enrolled subjects at the center or at least annually in addition to other criteria described in the study Monitoring Plan. Trained personnel or delegates appointed by the study Sponsor will perform study monitoring in order to ensure that the investigation is conducted, recorded, and reported in accordance with: the aforementioned agreements, plans, and regulations. The Sponsor (or designee) must be allowed access to the subjects' files as per the informed consent at the investigator's site when so requested.

10.6.3 Routine Monitoring

The following factors will be taken into account when determining the frequency of the monitoring visits: subject accrual rate at each center, total number of subjects enrolled at each center, protocol deviations, risk-based assessments for the primary and secondary endpoints and study protocol compliance at each center as described in the study Monitoring Plan. Monitors will require direct access to subject medical records pertinent to the study (and study inclusion criteria), study management documents, regulatory documents and Subject Informed Consent documents, as well as other potential applicable records not listed here.

Monitors may ensure the Study Investigators maintain staff and facilities to conduct the clinical investigation safely and effectively. Monitors may conduct the following monitoring activities throughout the study:

- Verification that the current IRB-approved informed consent was signed and dated by each subject;
- Verification of documentation in the subject's record that informed consent was signed prior to participating in any study related assessments or procedures and that a copy of the signed and dated consent form was provided to the subject;
- Source documentation verification by reviewing the CRFs against source documentation for accuracy and completeness of information;
- Verification that subjects and donor lung met study enrollment criteria;
- Confirmation that the study is being conducted according to the study protocol and applicable regulations;
- Verification that study deviations are documented and reported;

- Verification that the procedures for recording and reporting adverse events and serious adverse events to the Sponsor are followed;
- Ensuring proper error correction;
- Verification of training documentation of all study personnel participating in study related activities;
- Reviewing all correspondence and regulatory documents, including confirmation of IRB -approved study protocol or amendments; and
- Resolution of outstanding issues and completion of assigned tasks will be documented by the monitors.

10.7 CASE REPORT FORMS AND STUDY RECORDS

Case report forms (CRFs) are used to transmit the information collected in the performance of this study to the Sponsor (or its designee) and to governmental agencies. CRFs must be completed for each subject enrolled. Systems for electronic CRFs will be properly designed, validated, and implemented prior to use.

A selected number of donor and subject variables are required data collected by the transplant center via the OPTN. A data sharing agreement may be developed with UNOS for electronic transfer of those data elements directly to the Sponsor for each enrolled subject/donor.

CRF general guidelines will be used to complete all CRFs. Subjects will be given identification numbers so that their identity cannot be determined by the Sponsor and donor data will be identified for use by their UNOS ID. The research coordinator will keep a Master Subject List that will equate the identifiers to the actual donors and subjects that are a part of this study. This list will be kept in a secure location and will not be part of the Sponsor's regulatory documents. This information will only be made available to the Sponsor and/or their designee for routine verification of CRFs and also to the FDA if required for regulatory affairs.

The Investigator will review the CRFs for completeness and accuracy and sign and date the forms where indicated. Questions regarding missing or uninterpretable data will be communicated to the Principal Investigator/study coordinator for resolution and entered into a CRF correction form. The CRF correction form(s), after resolution of discrepancies, will be signed by the Principal Investigator and the revised data entered into a database. All records which support CRFs of this study or follow up must be retained in the files of the Principal

Investigator for a minimum of two years or until notification by the Sponsor, whichever is earlier.

10.8 DATA MONITORING COMMITTEE

A DMC, independent of the Sponsor, will be established for the study. Operating under a formal charter, the DMC will be comprised of four members: three physicians knowledgeable in lung transplantation, with at least one lung transplant surgeon and one transplant pulmonologist, and one statistician. Throughout the course of the study the DMC will meet regularly to monitor the safety of the subjects in the study. The DMC will be tasked with protecting the overall safety of the subjects in the study as well as advising the sponsor on potential decisions for stopping the study prematurely concerning either EVLP futility or effectiveness as observed in this study.

10.9 CLINICAL EVENTS COMMITTEE

A separate committee, independent of the Sponsor or DMC, will be charged with adjudicating the relatedness of SAEs to EVLP, transplantation and ECMO usage as well as all deaths reported for a determination of lung graft-related mortality. This Clinical Events Committee will be comprised of three members: three physicians knowledgeable in lung transplantation, with at least one lung transplant surgeon and one transplant pulmonologist. Adverse event adjudication will be performed separately from any DMC activities and will be blinded to treatment group to the extent possible for an open label, unblinded study. The CEC will be responsible for a retrospective adjudication of all events reported in the study thus far, previously reviewed by the DMC subcommittee under the earlier versions of this protocol, and all newly reported events and deaths.

10.10 PROTOCOL DEVIATIONS

A study deviation is defined as an event where the Study Investigator or site personnel did not conduct the study according to the study protocol, applicable laws or regulations or the Investigator agreement.

Prior approval by the Sponsor is expected in those situations in which the Investigator anticipates, contemplates, or makes a conscious decision to depart from procedures specified in the study protocol, except when necessary to protect the life or physical well-being of a subject

in an emergency. Prior approval is not expected in situations where unforeseen circumstances are beyond the Investigator's control (e.g., inadvertent mistakes, equipment failure, subject unable to do required testing due to illness).

All study deviations will be reported to the Sponsor and include a description of the deviation, justification for the deviation, and corrective action for the deviation. Study deviations may be discovered through a variety of sources, such as during the CRF review, telephone conversations, and site monitoring. Study deviations should be reported to the applicable IRB in accordance with IRB policies and/or local laws. When relevant, ethics committees, competent authorities or the appropriate regulatory bodies should be informed. The Sponsor will review all deviations from the study protocol. Corrective action and preventative action will be performed after protocol deviations are discovered during monitoring visits.

Deviations will be reported to the Sponsor regardless of whether medically justifiable, pre-approved by the Sponsor or taken to protect the subject in an emergency. Study deviations should be reported as soon as possible upon notification of the deviation. Investigators must notify the Sponsor and reviewing IRB per the IRB guidelines. Examples of deviations from the study protocol may include:

- No informed consent prior to transplant within a study subject;
- Incorrect version of consent provided to subject;
- Enrollment of subject prior to IRB approval;
- Enrollment of subject during an IRB approval lapse;
- Subject did not meet inclusion/exclusion criteria;
- Required testing and/or measurements not performed;
- Source data permanently missing;
- Serious Adverse Event not reported by Investigator in the required regulatory time frame; and
- Unauthorized physician performed study procedures (e.g. implanting physician was not an Investigator).

10.11 ACCESS TO SOURCE DOCUMENTATION

Each participating site will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of the Sponsor and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of QA reviews, audits, and evaluation of the study safety, progress and data validity.

Procedures and data collection will be documented utilizing site Standard Operating Procedures or will be captured in site generated worksheets and data collection forms considered source documentation. Source documentation is defined as original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Source document worksheets may be used to facilitate data collection. The center may create source worksheets or use ones provided by the Sponsor or Sponsor's representative. The worksheets may be used in conjunction with other center documentation. Source worksheets shall be provided for the EVLP data collection and post-EVLP evaluations. During the study, it may be necessary to provide additional worksheets to the Study Center. This may occur without a formal process or written notification.

During the study, the use of the CRF as the original entry or source may occur if approved by the Sponsor. This agreement shall be documented in writing and filed with the protocol in the Investigator study file. The original data will be collected onto source documents (either the subject's chart or a separate research subject chart that is kept in the research department) by the research site coordinator. This information will then be transcribed to the CRFs provided by the Sponsor for use in this study.

10.12 DATA GENERATION AND ANALYSIS

The Investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data (Section 10.10). The Investigators will maintain adequate case histories of study subjects, including accurate CRFs, (Section 10.7) and source documentation.

All donor identifying data will be redacted for the Sponsor and participating Investigators according to OPTN Policy 16 [OPTN 2020] and only unique UNOS ID# shall be used to connect the donor to the recipient (subject).

10.12.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the Investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff who will ensure that they are accurate and complete. Unanticipated problems and AEs must be reviewed by the Investigator or designee.

10.12.2 Data Capture Methods

10.12.2.1 Donor Data

Donor lung data will be provided by the OPO and/or Study Centers through secure-access (read-only) online database ('DonorNet') and/or through a paper-based medical record that accompanies the lung, or copies of donor information forwarded via electronic mail or facsimile. Relevant data will be transcribed into the Sponsor's CRF.

10.12.2.2 EVLP Data

EVLP procedure data will be recorded by the Sponsor during the clinical EVLP procedure. Data will be collected electronically in a secure online medical database (CMX). Relevant data will be transcribed into the Sponsor's CRF.

10.12.2.3 Subject (Recipient Data)

Subject data will be collected by participating Study Centers using the Sponsor's CRF.

10.13 RETENTION OF DATA

10.13.1 Retention of Study Documents

Study documents should be retained for a minimum of two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least two years have elapsed since the formal discontinuation of clinical development of the investigational device. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

10.13.2 Future Use of Stored Specimens and Other Identifiable Data

Donor lung biopsies and EVLP perfusate samples will be obtained and stored for potential future use. Donor lung biopsies and perfusate samples will be identified only by UNOS ID#.

Donor next of kin will provide authorization for research use of the donor lung tissue and samples taken during the EVLP process. Additionally, subject consent includes a statement that pre-transplant donor lung “biopsies (about the size of your small finger) may be taken using a surgical stapler,” and that “Pieces of lungs may also be removed with staplers from standard organ donors as well.”

10.14 FINANCIAL DISCLOSURE

Per 21 CFR 54, all Investigators are required to complete a Financial Disclosure form prior to site activation, attesting to the fact that they are unaware of any financial conflicts of interest, or disclosing potential conflicts, including payments, proprietary interests and/or equity interests. Completed forms will be maintained in the Trial Master File.

10.15 PUBLICATION AND DISCLOSURE POLICY

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical

procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and AEs. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. The Sponsor will register this study in ClinicalTrials.gov within 30 days of study start, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the Sponsor or designated Principal Investigator) register and report results of certain "applicable clinical trials:"

The Sponsor will develop subsequent publication policies prior to locking of the study data.

10.16 STUDY CLOSURE

Study closure is defined as a specific date that is determined by study completion and/ or regulatory requirements have been satisfied per the study protocol and/or by decision of the Sponsor or FDA. Study closure visits will be conducted at all enrolling Study Centers in order to review record retention requirements with site personnel. A telephone contact may take the place of a study closure visit if appropriate (e.g., low subject enrollment, recent monitoring visit).

Monitoring visits will be conducted by trained monitors and designees.

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Appendix 1 Schedule of Events

Evaluation	Screening Days -365 to -1	Baseline; Day 0	Post-Intervention Period							Follow-up
			Visit 1 (ICU); 24hr ± 6	Visit 2 (ICU); 48hr ± 6	Visit 3 (ICU); 72hr ± 6	Visit 4; Day 30 ± 5 dd	Visit 5; Day 90 ± 10 dd	Visit 6; 6 mon ± 14dd	Visit 7; 12 months ± 30dd	Premature Discont'n
Signed Informed Consent ^b	X	X	-	-	-	-	-	-	-	-
I/E Criteria	X	X ^a	-	-	-	-	-	-	-	-
Donor data collection ^c (Sponsor responsibility)	-	X	-	-	-	-	-	-	-	-
EVLP data collection ^d (Sponsor responsibility)	-	X	-	-	-	-	-	-	-	-
Demographics/Medical History	X	X ^a	-	-	-	-	-	-	-	-
Physical Examination	-	X ^a	-	-	-	-	-	-	-	-
Study intervention (dates and times for hospital admission, lung transplant, ICU admission)	-	X	-	-	-	-	-	-	-	-
Post-transplant Assessments (Study Investigator)										
X-ray, PaO ₂ and FiO ₂ (for PGD Scoring); O ₂ saturation	-	X	X	X	X	-	-	-	-	-
CLAD Status	-	-	-	-	-	-	X	X	X	(X)
FEV ₁	-	-	-	-	-	-	X	X	X	(X)
Oxygen required at rest	-	-	-	-	-	X ^e	X	X	X	(X)
ICU discharge date/time	-	-	-	-	(X)	(X)	(X)	(X)	(X)	(X)
Extubation date/time	-	-	-	-	(X)	(X)	(X)	(X)	(X)	(X)
Hospital discharge date	-	-	-	-	-	(X)	(X)	(X)	(X)	(X)
Hospital readmission date	-	-	-	-	-	(X)	(X)	(X)	(X)	(X)
Physical capacity	-	-	-	-	-	-	X	X	X	(X)
Work status	-	-	-	-	-	-	X	X	X	(X)

Centralized Lung Evaluation System
Clinical Trial Protocol: EVP-DEV-LTX-301, v4.0

Lung Bioengineering Inc.
28 JAN 2021

Evaluation	Screening Days -365 to -1	Baseline; Day 0	Post-Intervention Period							Follow-up
			Visit 1 (ICU); 24hr ± 6	Visit 2 (ICU); 48hr ± 6	Visit 3 (ICU); 72hr ± 6	Visit 4; Day 30 ± 5 dd	Visit 5; Day 90 ± 10 dd	Visit 6; 6 mon ± 14dd	Visit 7; 12 months ± 30dd	Premature Discont'n
Adverse event assessment	-	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Survival Assessment	-	-	-	-	-	X	X	X	X	(X)

Abbreviations: CLAD=Chronic Lung Allograft Dysfunction; dd=days; discont'n=discontinuation; FEV₁=forced expiratory volume in one second; FiO₂=fraction of inspired oxygen; hr=hour; ICU=intensive care unit; I/E=inclusion/exclusion; mon=months; PaO₂=partial pressure of oxygen in arterial blood; PGD=primary graft dysfunction; wks=weeks

Note(s): (x)=indicates "if applicable or as appropriate"

^a Data to be collected within 24 hrs prior to lung transplant.

^b Informed consent provided by the subject up to one year in advance and confirmed up to 24 hrs in advance of the lung transplant if required (Section 10.4).

^c Collection of donor demographics and suitability data. Confirm donor lung inclusion/exclusion criteria (Section 7.2.1.1).

^d Collect EVLP case data to determine transplant suitability and lung inclusion/exclusion criteria (Section 7.2.1.3).

^e At the time of discharge.

Appendix 2 Non-reportable Events

- Surgical
 - Anesthesia related nausea/vomiting
 - Surgical incision, thoracotomy, incision-related pain and bleeding
 - Moderate bruising at surgical site
 - Chest tube placement, chest tube pain
 - Surgical lines, including arterial, Swan-Ganz catheter, triple lumen catheter
 - Ventilator use during and after surgery
 - Back pain related to operating room table or referred pain
 - Cautery lesions in the skin
- Gastrointestinal
 - Nausea/vomiting
 - Constipation
 - Diarrhea
 - Gastroparesis
 - Hematemesis
 - Melena
 - *C. difficile* colitis
 - Gastritis
 - Esophagitis
 - Gastric/duodenal ulcer
 - Decreased appetite
 - Gastroesophageal reflux disease
 - Ileus
 - Partial intestinal obstruction
 - Malnutrition/anorexia
 - Systemic fever/pain/malaise/weakness
- Respiratory
 - Wheezing
 - Cough
 - Pleurisy
 - Pleural effusion
 - Pneumothorax
 - Hemothorax
 - Chylothorax
 - Hydropneumothorax

- Bronchospasm
- Diaphragmatic paralysis
- Intra-pulmonary shunt
- Bleeding secondary to biopsy
- Cardiovascular observations
 - Phlebitis
 - Clinically non-significant arrhythmias
 - Hypertension
 - Cold extremities
 - Pericarditis
 - Tamponade
 - Myocardial ischemia
 - Heart failure
 - Pericardial effusion
 - Peripheral edema
 - Hypotension
 - Hyperlipidemia
 - Deep vein thrombosis
- Neurological
 - Hallucinations
 - Confusion
 - Headaches
 - Insomnia
 - Psychosis
 - Neuropathy
 - Anxiety
 - Depression
 - Tremor
 - Visual disturbances
- Head/Eyes/Ears/Nose/Throat:
 - Sinusitis
 - Sore throat
 - Hoarseness
 - Paralyzed vocal cord
 - Cough
 - Epistaxis

- Thrush
- Herpes
- Renal/Genitourinary
 - Urinary tract infection
 - Urinary retention
 - Dysuria
 - Hematuria
 - Acute kidney injury
 - Azotemia
 - Dehydration
 - Electrolyte imbalance
- Hematological
 - Anemia
 - Leukopenia
 - Thrombocytopenia
 - Pancytopenia
 - Leukocytosis
 - Coagulopathy
- Musculoskeletal
 - Myopathy
 - Tendonitis
 - Deconditioning
 - Weakness
 - Osteoporosis
 - Fracture
 - Pain
 - Osteonecrosis
- Endocrinological
 - Osteopenia
 - Hyperglycemia or hypoglycemia in a diabetic patient
 - Diabetic ketoacidosis or hyperosmolar hyperglycemic state in a diabetic patient
 - Decreased testosterone
 - Vitamin D deficiency
 - Hyper/hypothyroidism
 - Adrenal insufficiency
 - Cushingoid changes

Notwithstanding the above, if an Investigator determines that, in the enrolled Subject population, the above Non reportable events are happening at a higher than expected frequency, or with more than the expected severity based on their clinical experience and judgment, the Investigator should report such AEs to the Sponsor. The above adverse events should also be reported if, in the opinion of the investigator, they could be related to the EVLP procedure despite their being listed above. If any of the events listed above are fatal, it should be reported as an SAE.

Appendix 3 EVLP Specialist Training Program

The technical staff consist of technicians and specialist that have been trained and qualified through the Sponsor's Training Program. EVLP Specialists candidates are selected from applicants having organ procurement and evaluation experience, including OPO personnel and surgeons. Specialist candidates are then qualified by a combination of intensive training with the development team at Toronto General Hospital, and a Sponsor-specific competency and qualification program upon their return.

Specialist candidates have extensive training in the TES through an in-residence program at TGH, culminating in successful completion of an Ex Vivo Lung Specialist Final Exam. This training program was developed by the team that developed the Toronto EVLP Method, and is therefore specifically focused on this mode of EVLP.

The practical, hands-on experience includes observing and participating in ongoing research (animal) EVLP procedures. Additionally, the specialist candidate will observe and participate in clinical (human) EVLP procedures performed at Toronto General Hospital.

The final exam includes oral and practical assessments while independently performing a research procedure using the TES to perfuse double swine lungs while being evaluated by a preceptor for the following skills:

- Assembly of the EVLP components into a working system.
- Troubleshooting all EVLP equipment.
- De-airing of the perfusion circuit.
- Calculation of lung flow and ventilation targets.
- Cannulation of the pulmonary artery and left atrium without leaks.
- Intubation of lungs with endotracheal tube.
- Performing retrograde flushing of the lungs prior to perfusion
- Placement of lungs on the EVLP circuit independently without kinks in the vessels or cannulas.
- Following correct sequence to warm up lungs.
- Turning on deoxygenation gas mixture at the correct time and ventilating lungs in the correct sequence.
- Operating and retrieving data from the Stöckert Centrifugal Pump Console (SCPC) pump, heater/cooler, pressure and temperature monitor, ventilator and ABG machine.

- Maintaining a lung on the TES.
- Cooling down lung in correct sequence.
- Removing lung and repackage independently.
- Explaining donor lung physiology and suitability for EVLP.
- Interpreting key assessment parameters during the EVLP procedure.

EVLP Technicians are specifically trained on the assembly of system components, documentation of EVLP procedures utilizing an electronic Batch Production Record, and performing surgical circulator and support functions. These personnel are directly trained and supervised by EVLP Specialists, and are subject to Qualification and ongoing competency assessment under the Sponsor's Training Program.

Appendix 4 Sample Size Determination Using Bayesian Approach with Power Prior

Sample size for this device trial is determined by the Bayesian approach with power prior (Ibrahim and Chen 2000, Pennello and Thompson 2008). Given two sets of historical 12 month survival data from the Sponsor's Traditional Feasibility study (IDE G140021; "a₀₁") and 2016-2018 Toronto EVLP data (Table A1; "a₀₂"), a sample size of 93 subjects would provide at least 80% power at a significance level of 0.1, with posterior probability of new device non-inferior than the control device (with a 0.08 margin; see Section 6.12) to be greater than 0.95.

A binomial-beta hierarchical model can be used to model the number of subjects y_t survived by year one in the new trial among n_t total subjects, and the underlying one-year survival rate p_t :

$$y_t|p_t \sim \text{Bin}(n_t, p_t), \quad \text{logit}(p_t) = \mu_t \sim \text{Beta}(a, b)$$

Under the assumption of power prior in the historical data with weights equal to a_{01} and a_{02} respectively, posterior distribution of μ_t is given by

$$\mu_t|y_t, y_{oc1}, y_{oc2} \sim \text{Beta}(y_t + a_{01}y_{oc1} + a_{02}y_{oc2} + a, n_t - y_t + a_{01}(n_{oc1} - y_{oc1}) + a_{02}(n_{oc2} - y_{oc2}) + b)$$

with y_{oci} to be the number of survived subjects in the historical trials among n_{oci} total subjects, $i=1,2$.

Sample size is determined using the simulated data from the posterior distribution. Appropriate values of hyperparameters a , b and the weights in power prior a_{01} and a_{02} are selected based on literature and all historical studies (Tables A2 and A3). The choice of a and b should be in accordance with historical studies in EVLP and other closely related studies. Given the justification for a combined survival endpoint of 0.80, as discussed in Section 6.12, and that the 12 months post-transplant survival rates from the historical EVLP studies are no less than 0.82, a combination of (a, b) with mean of the Beta prior distribution (hyper-mean) no less than 0.812 is a reasonable estimate. The difference of 12 months survival rate between the two historical datasets is about 7%, suggesting a standard deviation (hyper-sd) around 0.05 is reasonable. The choice of a_{01} and a_{02} depends on the similarity between the historical study and the new trial and

importance given to the historical datasets compared to the simulated data. With multiple historical datasets, the relative weight of historical dataset is also proportional to its sample size. Inclusion and exclusion criteria between the historical study and the new trial are compared respectively to assess trial similarity and importance of historical data relative to new trial is also evaluated. Scores of 0.6 and 0.4 can be assigned to the first and second historical data respectively, since the historical data is about 0.8 as important as the new design and the first and second historical data are about 80% and 50% similar to our new study respectively. The weight a_{02} should then be divided by 2 since the sample size ratio of the two historical studies is about 1:2 (66:120). Given above considerations, weights $a_{01} \approx 0.6$, and $a_{02} = 0.2$ are reasonable. Table A3 displays the sample sizes required for a margin varying from 0.08 to 0.10 with various weights and parameter combinations. The sample size of 93 and margin 0.08 is optimal in terms of the weights, standard deviation and Type I error estimate for the parameter combinations of (a,b).

Table A1 Historical EVLP Data

Study	Total N	Number Survived at 12 months	One-Year Survival Rate
Sponsor's Feasibility Study	66	59	89.4%
Toronto EVLP data (2016-2018)	120	99	82.5%

The choice of a_{01} and a_{02} depends on the similarity between the historical studies and the new trial and the importance given to the historical datasets compared to the simulated data. With multiple historical datasets, the relative weight of the historical dataset is also proportional to its sample size.

Table A2 Dataset Similarity

Consideration	Sponsor's Feasibility Study	TGH EVLP 2016-2018
Importance given to the historical datasets compared to the simulated data	0.8	0.8
Similarity with the historical studies: 1. Device used 2. Personnel 3. Perfusion procedure 4. Transplant centers 5. Recipient criteria 6. Donor/donor lung exclusion criteria 7. Donor/donor lung inclusion criteria	1. Identical device 2. Same personnel 3. Same EVLP facility and perfusion procedures 4. 7 common transplant centers 5. Inclusion/Exclusion criteria 90% similar (the Pivotal study allows enrollment of subjects on ECMO prior to transplant, or who are positive for hepatitis B or C, which are higher risk groups) 6. Donor lung exclusion criteria identical 7. Donor inclusion criteria: 44% of subjects enrolled with identical criteria to Pivotal. 56% enrolled with 95% similar criteria.	1. 95% identical device. 2. LBE personnel trained by Toronto Team 3. Different facility, same procedures. 4. Toronto data based on single-center experience vs multi-center trial. 5. Inclusion/Exclusion 80% similar 6. Donor exclusion criteria 90% similar 7. Donor inclusion criteria same as original Feasibility protocol
Similarity weight	0.8	0.5
the relative weight of historical dataset 66:120 (around 1:2)	1	2
a_0	$a_{01}=0.8*0.8=0.64$	$a_{02}=0.8*0.5/2=0.2$

Table A3 Sample Size Derivation

Margin	n	a₀₁	a₀₂	a	b	hyper- mean	hyper-sd	power	Type I error
0.08	93	0.6	0.2	34	8	0.810	0.060	0.80	0.086
0.08	93	0.5	0.2	33	7	0.825	0.059	0.80	0.086
0.08	93	0.5	0.2	29	6	0.829	0.063	0.80	0.086
0.08	93	0.5	0.2	34	7	0.829	0.058	0.80	0.086
0.09	75	0.6	0.2	37	9	0.804	0.058	0.82	0.096
0.09	75	0.5	0.2	42	10	0.808	0.054	0.82	0.096
0.09	75	0.6	0.2	42	10	0.808	0.054	0.82	0.096
0.09	75	0.5	0.2	34	8	0.810	0.060	0.82	0.096
0.09	75	0.6	0.2	43	10	0.811	0.053	0.82	0.096
0.09	75	0.5	0.2	44	10	0.815	0.052	0.82	0.096
0.1	60	0.5	0.2	40	10	0.800	0.056	0.81	0.095
0.1	60	0.5	0.2	36	9	0.800	0.059	0.81	0.095

Appendix 5 Reference Safety Information (RSI)

The below list of adverse events was previously observed in a Traditional Feasibility study conducted with the CLES device (reference IDE G140012)

- Acute lung injury
- Acute respiratory failure
- Anastomotic complication
- Bronchial anastomosis complication
- Bronchopleural fistula
- Bronchostenosis
- Complications of transplanted lung
- Dyspnoea
- Hypercapnia
- Hypoxia
- Infectious pleural effusion
- Pneumomediastinum
- Pneumonia
- Pneumothorax
- Procedural hypotension
- Pulmonary embolism
- Pulmonary hypertension
- Pulmonary hypoperfusion
- Pulmonary infarction
- Reperfusion injury
- Shock haemorrhagic
- Transplant Dysfunction
- Transplant Rejection
- Weaning failure

The events above are the Preferred Terms for the events considered as "Related" in the IDE Final Report for the Traditional Feasibility study dated 01 May 2020 (reference G140021/R031).

Some of the events reported as "related" in this annual report were NOT added to the RSI Datasheet because the PV Physician believes that there is no mechanism of action in the EVLP device to cause these events (e.g. Abdominal compartment syndrome, Cardiomegaly, Deep vein thrombosis, Left ventricular Dysfunction, Peripheral ischaemia, Ultrasound Doppler abnormal,

and Venous injury). The events of Pneumonia bacterial, Postoperative respiratory failure, and Respiratory failure were not included because they represent the same medical concepts as other events already included in the RSI and do not need to be listed separately.

It is important to note that for the sake of expedited reporting (UADE), every serious adverse event in the trial will be individually assessed by the sponsor and the Principal investigator, and a decision will be made with regards to expedited reporting independent of whether or not the event is listed as expected in the RSI.

The “As Determined Listedness” in the Sponsor’s database may then be updated based on the details of that particular event if applicable.

Appendix 6 Sponsor Signatures

Study Title: Increasing Lung Transplant Availability Using Normothermic Ex Vivo Lung Perfusion (EVLP) at a Dedicated EVLP Facility

Study Number: EVP-DEV-LTX-301 v. 4.0

Version Date: 28 January 2021

This clinical study protocol was subject to critical review and has been approved by the Sponsor.

The following personnel contributed to writing and/or approving this protocol:

Signed/Dated: _____

DocuSigned by:
Jacqueline Honig
Signer Name: Jacqueline Honig
Signing Reason: I have reviewed this document
Signing Time: 28-Jan-2021 | 6:45:13 PM EST
6A926B94EFE2445683F72A0BFBEAAE24

Jacqueline Honig, MD
Medical Director

Signed/Dated: _____

DocuSigned by:
Michael Roberts
Signer Name: Michael Roberts
Signing Reason: I approve this document
Signing Time: 29-Jan-2021 | 6:22:44 AM EST
8E64BB55BBF14332BEE05B5ADA2553B3

Michael Roberts, MA, RAC
Director, Regulatory Affairs

Appendix 7 Investigator's Signature

Study Title: Increasing Lung Transplant Availability Using Normothermic Ex Vivo Lung Perfusion (EVLP) at a Dedicated EVLP Facility
Study Number: EVP-DEV-LTX-301 v. 4.0
Version Date: 28 January 2021

The signature below indicates the approval of this protocol and its appendices, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:

Signed: _____ Date: _____
Printed
Name: _____
Title: _____
Institution: _____