



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

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STATISTICAL ANALYSIS PLAN

Version 2.0

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Version 2.0

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ABBREVIATIONS

ABG	Arterial Blood Gas
ADL	Activities of daily living
AE	Adverse Event/Adverse Effect
CI	Confidence Interval
CIT	Cold ischemic time
CLAD	Chronic Lung Allograft Dysfunction
CLES	Centralized Lung Evaluation System
CRF	Case Report Form
CRO	Contract Research Organization
DLT	Double-lung Transplant
ECMO	Extracorporeal Membrane Oxygenation
EVLV	Ex Vivo Lung Perfusion
EVP	Ex Vivo Perfusion
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in one second
FiO ₂	Fraction of inspired oxygen
FPFV	First patient, first visit
GDS	Global Drug Safety
ICU	Intensive Care Unit
LASDDG	Lung Allocation Score Disease Diagnosis Group
LAS	Lung Allocation Score
LBE	Lung Bioengineering, Inc.
LBT	Lung Biotechnology PBC
LOS	Length of stay
LPLV	Last patient, last visit
MedDRA®	Medical Dictionary for Regulatory Activities
OPO	Organ Procurement Organization
OPTN	Organ Procurement and Transplantation Network
PaO ₂	Partial pressure of oxygen in arterial blood
PGD	Primary Graft Dysfunction
PGD3	Pulmonary Graft Dysfunction 3
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Effect
SAP	Statistical Analysis Plan
SD	Standard deviation
SLT	Single-lung Transplant
SOC	System Organ Class
UADE	Unanticipated Adverse Device Effect
US	United States
UTC	United Therapeutics Corporation

SAP REVISIONS

Version 1.0 of the SAP was finalized at the time of Protocol version 2.0 (26JUL2018). The following table details the changes made to the SAP.

Revision History			
SAP Version #	SAP Section	Modification	Description and Rationale
1.0		Original Version	N/A
2.0	1	Added “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%.”	Protocol version 4 update
2.0	2.1.1	Changed ‘6 months’ to ‘12 months’	Protocol version 4 update
2.0	2.1.2	Added “Adjudicated lung graft-related mortality measured as the percentage of study subject deaths determined to be related directly or indirectly to the transplanted organ” Added “6 months” to “subject survival at ...” Changed “days” to “hours” and added “prior to initial hospital discharge” to “Duration of subject ventilator ...” Added “measured as number of subjects diagnosed with CLAD post-transplant” to “Rate of diagnosis ...” Added “at defined timepoints” to “Forced expiratory volume ...”	Protocol version 4 update
2.0	2.2.1	Replace “combined incidence of six months mortality and mortality prior” and replaced with “freedom from mortality at 12 months and prior”	Protocol version 4 update

Revision History			
SAP Version #	SAP Section	Modification	Description and Rationale
2.0	2.2.2	Added “Adjudicated lung graft-related mortality measured as a percentage of study subject death determined to be related directly or indirectly to the transplanted organ” Added “Subject survival at 6 months post-transplant” Updated “Time to first cessation of recipient ventilator support, measured as total number of days post-transplant ventilator support is required” to “Duration of subject ventilator support, measured as total number of hours post-transplant ventilator support is required prior to initial hospital discharge” Added “measured as the proportion of subjects that require ECMO support for any reason and at any time prior to initial hospital discharge after transplantation” to “Rate of ECMO ...” Added “Extended evaluation and “ to “Preservation time, ...” Added “measured as the number of subjects diagnosed with CLAD post-transplant” to “Rate of CLAD ...” Replaced “values at defined time points” with “30 days, 90 days, 6 months and 12 months post-transplant” in “FEV₁ values ...”	Protocol version 4 update

Revision History			
SAP Version #	SAP Section	Modification	Description and Rationale
2.0	3.1	Added “a prospective, multi-center” Replaced “A sample size of 186 subjects ...” with “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); all 75 control subjects will be matched to a unique EVLP subject. At least 25 of subjects in the control group must undergo SLT and be matched to a corresponding EVLP subject undergoing SLT; and similarly, at least 25 subjects in the control group must undergo DLT and be matched to a corresponding EVLP subject undergoing 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” Reference to “6 months” was updated to “12 months” Replaced “Subsequently, all patients will be followed ...” with “Subsequently, recipient data will be collected from the Federal OPTN database for five years post-transplant to monitor long-term survival and safety events. These long-term data are not being collected under the Investigator Device Exemption (IDE) protocol and are not subject to the statistical analyses presented herein. Study assessments will be performed as outlined in the Schedule of Events (Appendix 11.1)	Protocol version 4 update. Added text to clarify sample size in each group and matching based on transplant type

Revision History			
SAP Version #	SAP Section	Modification	Description and Rationale
2.0	3.2	updated “e.g. from donor lung retrieval to the end of CIT2) must not be greater than a combined 22 hrs” to “i.e., from donor lung retrieval to the start of EVLP (CIT-1), EVLP observation time (EVLP), and from the end of EVLP to the start of lung transplantation (CIT-2)) must not be greater than a combined 22 hours”	Additional text to clarify CIT-1 and CIT-2.
2.0	3.2.1	Removed “Randomization Scheme and” from section header Replaced “inclusion criteria” with “inclusion and exclusion criteria” Removed “each” in “In this way, ...” and added “until 75 EVLP subjects have been matched” Replaced “eliminate” with “minimize” in “The first eligible ...” Replaced “more” with “less”, “two thirds” with “one-third”, added “matched”, changed “44” to “25”	To add clarity to treat arm assignment
2.0	3.2.3	Added “(or initial hospital discharge date, if later)” Replaced “6 months” with “their 12 month” Added “follow-up visit and all ongoing SAEs or AEs have been followed for 30 days after the last Study Center visit, whichever is later, and all queries have been resolved.” Changed “24” to “36”	Protocol version 4 update.
2.0	4	Deleted “Two-sided 95.0% confidence intervals (CIs) will be provided for the primary and secondary endpoints, as appropriate to the data” Added “When applicable, listings will be additionally sorted by visit and assessment date/time”	Updated text to align with how data will be presented

Revision History			
SAP Version #	SAP Section	Modification	Description and Rationale
2.0	4.1	Section header updated to “Analysis Quality Control Procedures” Deleted text that is not applicable to current process	Updated text to match current process
2.0	4.2	Replaced “Two” with “Three” Added definition for Matched Analysis Set Clarified definitions for the Full Analysis Set and Ancillary Populations	Add clarity to the analyses set definitions
2.0	4.4	Changed “6” to “12” and added “if later”	Protocol version 4 update
2.0	4.5	Updated to “No adjustments for multiple comparisons are being made because none of the secondary endpoints will be evaluated using formal tests of hypothesis”	Expanded text on reason for no adjustments for multiple comparison
2.0	5.1	Updated “A table of counts of subjects in the FAS” to ” A table of counts and percentages of subjects in the FAS, MAS and APS” Added “The number of potential subjects screened but not enrolled will be presented. A by-subject listings will also be provided”	To clarify analysis population for listing and summary
2.0	5.2	Added “for the APS” and “in descending order”	To clarify analysis population for listing and summary
2.0	5.3	Updated “FAS” to “APS and MAS”	To clarify analysis population for listing and summary

Revision History			
SAP Version #	SAP Section	Modification	Description and Rationale
	5.3	Added “and BMI (kg/m ²) Added “Other parameters as collected (e.g., pulmonary artery pressure, vascular resistance, O2 saturation, peak airway pressure)” to EVLP Information	Protocol version 4.0 update
	5.4	Replaced “ending” with “present” Delete “EVLP” Replaced “PT. The data will also be listed.” With “in descending order for PT for the APS. The data will also be provided in a subject listing.”	To clarify analysis population for listing and summary
	5.5	Added “in descending order” Added “for the APS”	To clarify analysis population for listing and summary
	6.1	Section header changed to “Analysis of Primary Endpoint”	Protocol version 4 update
	6.2	New section	Additional analyses to be performed in support of the primary endpoint
2.0	6.3	Previously section 6.2 Updated section header to “Analyses of Secondary Endpoints”	Moved to section 6.3 due to the addition of a new section for 6.2
	6.4	New section	Additional analyses to be performed in support of the primary and secondary endpoints

Revision History			
SAP Version #	SAP Section	Modification	Description and Rationale
	7	Added “All safety analyses will be based on the APS”	Clarify analyses population for Safety
	7.2	Added “from transplanted organ reperfusion through 90 days post-transplant, and all serious adverse events (SAEs) will be recorded” to “AEs will be recorded ...”	Protocol version 4 update
	7.2.3	Removed “but additional information may be obtained” Added “If the relationship of an AE/SAE is determined to be “Possibly Related” or “Related” the event will be considered to be related for the purposes of expedited regulatory reporting. An assessment of “Unlikely” will be considered “Not related”.”	Added to clarify when creating a summary table of “Related” vs “Not Related”
	7.2.4	Removed “serious adverse event”	The abbreviation for SAE has been used prior to this section
	7.2.5	Removed “for the FAS” Deleted summary for : “the number and percentage of subjects experiencing an intervention-emergent AE leading to study withdrawal” Added summaries for: “the number and percentage of subjects experiencing an intervention-emergent AE by strongest relationship to EVLP” “the number and percentage of subjects experiencing an intervention-emergent AE by strongest relationship to ECMO”	Additional summaries to be provided

Revision History			
SAP Version #	SAP Section	Modification	Description and Rationale
	7.3	Added “samples” Replaced “thereafter” with post-transplant	Protocol version 4 update and clarify text
	7.4	Added “A by subject listing will be provided.”	To clarify what summary will be provided
	9.1	Section header changed to “12 Month Survival” Added “The primary endpoint for this trial has evolved with each revision of the study protocol. Originally (protocol version 1.0, dated 25 January 2018), 30-day survival was the primary endpoint with 66 EVLP subjects required. Version 2.0 of the protocol (dated 26 July 2018) modified the primary endpoint to 6-month survival with an increase in the sample size of the EVLP group to 93. Version 3.0 of the protocol (dated 25 February 2020) modified the primary endpoint to 12-month survival, introduced the use of a Bayesian analysis, and set a performance goal that the point estimate of 12-month survival would be required to exceed 80.2%, for a decrease to the sample size of the trial with 75 EVLP subjects needed. Version 4.0 of the protocol (dated 28 January 2021) continued the use of a Bayesian analysis, and modified the performance goal to 81.2, while allowing for a sample size of the trial with 93 EVLP subjects needed...”	To clarify the primary endpoint and relation to protocol changes
	9.2	Removed “and estimation of Control group parameters for design of future studies” Replaced “will be 93” to “of 75” Removed “and subjects will be matched to the EVLP Group for similarity”	Protocol version 4 update

Revision History			
SAP Version #	SAP Section	Modification	Description and Rationale
	9.3	Deleted section	Update to align with analysis for the primary endpoint
	10	Updated references	Updated to reflect references specified in the body of the SAP

1. INTRODUCTION

This document details the Statistical Analysis Plan for study Protocol EVP-DEV-LTX-301, an unblinded, non-randomized, pivotal study to evaluate the effectiveness and safety of the Centralized Lung Evaluation System (CLES) among subjects undergoing lung transplant using lungs after EVLP performed exclusively by Lung Bioengineering Inc (the Sponsor) at a Sponsor facility.

Lung Bioengineering Inc. (LBE) is the sponsor of the EVP-DEV-LTX-301 study. Lung Bioengineering is a wholly owned subsidiary of Lung Biotechnology PBC (LBT). LBE is responsible for regulatory filings, medical monitoring, and managing the EVLP facility. LBT is responsible for clinical operations oversight, clinical data management oversight, statistical oversight and program management support. LBT is a wholly owned subsidiary of United Therapeutics Corporation (UTC). Global Product Safety & Pharmacovigilance (formerly UTC GDS, now GPS&PV) provides safety reporting and oversight responsibilities on this study and is a department within the parent company, United Therapeutics Corporation.

Lung transplantation is often the only available therapy for patients suffering from 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 demands 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 who are used for transplanting other solid organs.[1]

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.[2] Technologies such as EVLP might facilitate assessment of lung condition, thereby enabling transplant programs to use lungs for transplant that are currently discarded.

In 2015, 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 CLES with lungs that did not meet standard lung donation criteria or were otherwise unable to be used for traditional transplantation. The CLES is identical to the equipment used to gain Health Canada approval in 2014 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 Grade 3 (PGD3) at 72 hours post-transplant and 30-day mortality. The results of this study suggest acceptable rates of PGD3 at 72 hours and no 30-day mortality. Furthermore, similar outcomes in terms of post-transplant patient and graft survival at longer post-transplant time points 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%.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

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 the subject survival at the later of 12 months or first hospital discharge post-transplant.

2.1.2 Secondary Objectives

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 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
- Forced expiratory volume in one second (FEV₁) at defined timepoints.
- The above information will also be collected on patients enrolled in a contemporaneous control group to evaluate similar findings among recipients of lungs not evaluated during EVLP.

2.2 Endpoints

2.2.1 Primary Endpoint

The primary endpoint of the study is post-transplant survival measured as the freedom from mortality at 12 months and prior to first hospital discharge after the lung transplant procedure.

2.2.2 Secondary Endpoints

Secondary endpoints include the following:

- Adjudicated lung graft-related mortality measured as a percentage of study subject death 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, 28 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;
- ICU 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 prior to initial 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 CLAD measured as the number of subjects diagnosed with CLAD post-transplant;
- Rate of respiratory failure; and

- FEV₁ at 30 days, 90 days, 6 months and 12 months post-transplant.

3. INVESTIGATIONAL PLAN

3.1 Study Design

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, match to a donor lung offer through the standard Organ Procurement and Transplantation Network (OPTN) allocation system, and meet the other eligibility criteria, 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. 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 (LAS Disease Diagnosis Group “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); all 75 control subjects will be matched to a unique EVLP subject. At least 25 of subjects in the control group must undergo SLT and be matched to a corresponding EVLP subject undergoing SLT; and similarly, at least 25 subjects in the control group must undergo DLT and be matched to a corresponding EVLP subject undergoing 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.

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. Each control subject must demonstrate similar “matching” to a subject enrolled in the Study from the same Center who receiving 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 hospital discharge, if later) and any required follow-up for Severe Adverse Events (SAEs) or AEs.

Following transplantation, subjects will be admitted to the ICU, and the initial 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 hours for the next 72 hours. 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. These long-term data are not being collected under the Investigator Device Exemption (IDE) protocol and are not subject to the statistical analyses presented herein. Study assessments will be performed as outlined in the Schedule of Events (Appendix 11.1).

3.2 Treatment

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 geographic 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 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 in situ 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 hours, 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 (i.e., from donor lung retrieval to the start of EVLP (CIT-1), EVLP observation time (EVLP), and from the end of EVLP to the start of lung transplantation (CIT-2)) must not be greater than a combined 22 hours within individual phase limits as follows:

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

The preservation time for the second lung being transplanted (i.e., from donor lung retrieval to the end of CIT-2) must not be greater than a combined 26 hours within individual phase limits as follows:

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

3.2.1 Treatment Arm Assignment

All patients who have provided informed consent to participate in this study will be screened, and eligibility will be assessed according to applicable Inclusion and Exclusion Criteria. 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. 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 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 and Exclusion Criteria.

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 EVLP Group subject enrolled at their site until 75 EVLP subjects have been matched. Control matching must take place as each patient is 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 minimize 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 contract research organization (CRO), using site-specific identification and coding assigned per the case report form (CRF) Completion Guidelines. Recipient data provided to the Sponsor or the CRO 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.

3.2.2 Blinding

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

3.2.3 Duration of Subject Participation

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 initial hospital discharge date, if later). The database will be locked for analysis once the last subject enrolled reaches their 12 month (or initial hospital discharge date, if later) follow-up visit and all ongoing SAEs or AEs have been followed for 30 days after the last Study Center visit, whichever is later, and all queries have been resolved. 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.

3.2.4 Subject 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.

4. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

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 (SDs), 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.

The database will be locked for analysis of endpoints after the last subject completes his/her last Study Center visit and all on-going SAEs or AEs have been followed for 30 days after the last Study Center visit, as required per this protocol, whichever is later, and all queries have been resolved.

Analyses will be performed using SAS for Windows statistical software, version 9.4 or higher (SAS, Cary, NC), except where other software may be deemed more appropriate.

CTI Clinical Trial and Consulting Services (Cincinnati, OH) will perform all efficacy and safety statistical analyses.

The results will be presented by Treatment Group, specifically by transplant subtype (SLT or DLT) and Overall Treatment Group. The layout will be presented similar to that shown below:

EVLP			Control		
SLT (N=XX) n (%)	DLT (N=XX) n (%)	Overall (N=XX) n (%)	SLT (N=XX) n (%)	DLT (N=XX) n (%)	Overall (N=XX) n (%)

Subject data will be listed, sorted by Treatment Group, SLT or DLT, and subject number. When applicable, listings will be additionally sorted by visit and assessment date/time.

4.1 Analysis Quality Control Procedures

Once all the source verification is complete, all queries are resolved, and the database has been updated appropriately, the database will be locked and made available to CTI Biostatistics for final analysis.

Data may be pulled by CTI Biostatistics for the DSMB analysis at a time when source verification and query resolution is ongoing.

All SAS programs used to create analysis data sets, tables, and listings are double programmed. The SAS outputs will be compared, and the programs will be updated until the outputs match.

4.2 Analysis Sets

Three analysis sets will be considered for this study:

- Full Analysis Set (FAS): Includes all subjects in the EVLP group regardless of subject outcome or subsequent re-transplant. This population will be used for the primary and secondary endpoints and also used as supportive for safety analyses.
- Matched Analysis Set (MAS): Includes only subjects in the EVLP and contemporaneous control group to those who were matched by the protocol defined algorithm (see Section 5.3 of protocol). This population will be used as supportive for primary and secondary

endpoint, and safety analyses.

- Ancillary Population Set (APS): Includes all subjects who have received either a transplant by EVLP or standard of care. This population will be used for the safety analyses and also used as supportive for primary and secondary endpoints.

4.3 Assessment Windows

For the purpose of analyzing time to event endpoints, the time-in-study for each patient will be measured relative to Day 0, the day of transplantation.

For the purpose of listing and summarizing data, the time-in-study for each patient observation will be defined using study days. Such days will be measured relative to Day 0, the day of transplantation.

All data will be summarized by visit based on the visit in which the data was recorded in the database.

Baseline will be defined as the last pre-intervention value during the screening period. If more than one assessment exists within a single visit window, the value closest to the protocol study visit will be used for summary and analysis purposes. Data from all assessments will be listed.

4.4 Handling of Dropouts or 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.

4.5 Multiple Comparisons

No adjustments for multiple comparisons are being made because none of the secondary endpoints will be evaluated using formal tests of hypothesis.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

A table of counts and percentages of subjects in the FAS, MAS and APS will be provided. Reasons for not completing study as planned and reasons for premature withdrawal will be tabulated for the groups. The number of potential subjects screened but not enrolled will be presented.

A by-subject listings will also be provided.

5.2 Protocol Deviations

A listing of all protocol deviations will be provided for the APS. Distribution for the types of protocol deviations and the number of subjects that deviate from the protocol will be tabulated in descending order for the groups.

5.3 Demographic and Baseline Characteristics

Demographic data and baseline characteristics for all APS, and MAS 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.

Recipient Demographics and Baseline Characteristics

The following demographic variables for the recipient will be summarized:

- Sex, race, ethnicity, age (years) at time of transplantation
- Weight (kg), height (cm), and BMI (kg/m²)
- LASDDG
- ECMO status
- LAS at time of waitlist addition and at time of lung match

Donor Demographics and Characteristics

The following demographic variables for the donor will be summarized:

- Sex, race, ethnicity, age (years) at death
- Weight (kg) and height (cm)
- Primary cause, mechanism, and circumstances of death

EVLP Information

- Lungs received (single right, single left, bilateral)
- EVLP time (hours)
- Donor lung evaluation (met transplant inclusion criteria, accepted for transplant)
- Organs shipped
- Other parameters as collected (e.g., pulmonary artery pressure, vascular resistance, O₂ saturation, peak airway pressure)

Transplant Information

- Donor type
- Donor and recipient ABO blood group, “A” blood group subtype, Rh factor
- Lung type
- Lung inclusion criteria met
- Ventilation parameters (terminal PaO₂, tidal volume, FiO₂, PEEP, rate)
- Procurement information

5.4 Medical History

Medical history (medical conditions present prior to transplant) will be collected. All medical conditions and surgical procedures will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percent of subjects with each medical condition and surgical procedure will be presented overall and by transplant subtype for each SOC and in descending order for PT for the APS.

The data will also be provided in a subject listing.

5.5 Concomitant Medications

Concomitant medications will be documented for the 2-week period prior to the onset of a SAE. Concomitant medications will be coded using World Health Organization (WHO) drug classifications. The number and percent of FAS subjects using concomitant medications will be tabulated by Anatomical, Therapeutic, and Chemical (ATC) class, and in descending order by preferred name, transplant subtype and overall for the APS.

6. ENDPOINT ANALYSIS

6.1 Analysis of Primary Endpoint

Post-transplant survival will be defined as freedom from mortality at 12 months and prior to first hospital discharge.

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.

The primary endpoint analysis will be the 12-month survival rate. Presented will be the point estimate with associated 95% confidence interval. The FAS population will be used for this primary analysis.

6.2 Supportive Analyses for the Primary Analyses

The 12-month survival rates (with associated 95% confidence intervals) will be produced using the MAS and APS populations as supportive to the results of the primary analysis.

6.2.1 Centrally-Adjudicated Mortality

An independent adjudication committee (see CEC Charter) will review all deaths occurring in the trial to assign relatedness to EVLP and/or primarily caused by the lung graft failure.

The 12-month survival rates (with associated 95% confidence intervals) will be produced using the MAS, and APS populations by EVLP-relatedness and primarily caused by the lung graft failure.

If the relatedness to EVLP is determined to be “Possibly Related” or “Related” the event will be considered to be related for the purposes of expedited regulatory reporting.

6.2.2 Bayesian Analysis

Previously stated as the primary endpoint analysis, but now supportive, an evaluation will be conducted as to whether the 12-month survival rate in the EVLP group is greater than the performance goal of 81.2% using the FAS population. Success will be achieved if the posterior probability is greater than 0.95. The posterior distribution of p_t is given by

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

where: n_{oci} = total subjects in the historical trials among $i = 1, 2$ ($n_{oc1}=66$, $n_{oc2}=120$)

y_{oci} = number of survived subjects at one year in the historical trials among, $i=1, 2$ ($y_{oc1}=59$, $y_{oc2}=99$)

a_{0i} = selected weights in power prior for historical trials, $i=1, 2$ ($a_{01}=0.6$, $a_{02}=0.2$)

y_t = number of subjects survived at 12 months

n_t = total number of subjects ($n_t=93$)

a and b are hyperparameters ($a = 34$, $b = 8$)

Refer to appendix 11.2 for complete details.

The proportion of subjects and two-sided 90% confidence interval surviving through 12 months and first hospital discharge after transplant will also be provided by Transplant Group.

Other supportive summary statistics 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 using Kaplan-Meier survival probability plots.

6.3 Analyses of Secondary Endpoints

The secondary endpoints will be presented using descriptive statistics without hypothesis testing.

Results may be displayed graphically. 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 along with 95% CI
- 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 along with 95% CI.
- 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 along with 95% CI;
- Subject survival at 90 days post-transplant along with 95% CI;
- Subject survival at 6 months post-transplant along with 95% CI;
- Subject survival at 12 months post-transplant along with 95% CI;

- 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;
- ICU 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 prior to discharge post-transplant;
- Extended evaluation of preservation time, defined as the elapsed time between donor aortic cross clamp time 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 AEs;
- Rate of respiratory failure along with 95% CI;
- Rate of CLAD measured as the number of subjects diagnosed with CLAD post-transplant; and
- FEV₁ at 30 days, 90 days, 6 months and 12 months post-transplant.

6.4 Subgroup Analyses

Primary and secondary endpoints will also be presented as relevant for evaluation of outcomes for the following subgroups within the EVLP and Control Groups:

- center enrollment numbers (quartiles)
- single- or double-lung transplantation
- cold ischemic time 1 (CIT-1) (median split)
- EVLP observation time (EVLP) (median split)
- cold ischemic time 2 (CIT-2) (first lung and second lung; median split)
- total preservation time (first and second lung; median split)
- donor lung criteria (standard vs expanded)
- donor lung source (OPO vs transplant center referral)
- use of pre-operative recipient ECMO (use versus non-use)

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

- Standard and extended criteria have been adopted from recent published literature and adapted to account for the Exclusion Criteria listed in Section 5.2.2 of the protocol [Copeland, 2020; Christie, 2021]. Extended criteria donor lungs are defined as those meeting the following criteria:
- DCD; or
- Two or more of the following:
 - Final PaO₂/FiO₂ ratio less than 300
 - Age at death over 55 years
 - Greater than or equal to 20 pack-year smoking history
 - Diabetes mellitus diagnosis
 - Evidence of blood infection
 - Abnormal chest radiograph or computed tomography
 - Evidence of pulmonary edema

Any donor lungs not meeting the extended criteria are considered “standard criteria” for the purposes of the subgroup analysis. The above data are collected and reported via standard organ donor screening processes.

7. SAFETY ANALYSIS

Safety analyses to be performed include adverse events, clinical laboratory assessments, and physical examinations. All safety analyses will be based on APS.

7.1 Extent of Exposure

This is not applicable since no investigational drug will be used in the study.

7.2 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.

AEs will be recorded from transplanted organ reperfusion through 90 days post-transplant, and all serious adverse events (SAEs) will be recorded throughout the study. AEs and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

7.2.1 Intervention-emergent Adverse Events

Intervention-emergent AEs will be defined as those events that are newly occurring or worsening from Baseline (Day 0). In all cases, only intervention-emergent AEs will be summarized.

7.2.2 Adverse Event 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.

7.2.3 Adverse Event Relationship to Study Intervention

The relationship of an AE to EVLP procedure and lung transplant will 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 procedures seems not relevant and/or the event can be reasonably explained by another cause.
- **Not related:** There is no temporal relationship between the investigational device or procedure and the event onset, an alternate etiology has been established.

If the relationship of an AE/SAE is determined to be “Possibly Related” or “Related” the event will be considered to be related for the purposes of expedited regulatory reporting. An assessment of “Unlikely” will be considered “Not related”.

7.2.4 Serious Adverse Events

A 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.

7.2.5 Adverse Event Summaries

Adverse events and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. For intervention-emergent AEs, the following will be summarized and presented by Transplant Group

- i. An overall summary of Intervention-emergent AEs, which includes:
 - a. the number and percentage of subjects experiencing an intervention-emergent AE
 - b. the number and percentage of subjects experiencing an intervention-emergent AE by strongest relationship to lung transplant

- c. the number and percentage of subjects experiencing an intervention-emergent AE by strongest relationship to EVLP
- d. the number and percentage of subjects experiencing an intervention-emergent AE by strongest relationship to ECMO
- e. the number and percentage of subjects experiencing an intervention-emergent AE by greatest severity
- f. the number and percentage of subjects experiencing an intervention-emergent SAE
- g. the number and percentage of subjects experiencing an intervention-emergent non-SAE
- h. the number and percentage of subjects experiencing an intervention-emergent AE leading to study withdrawal
- ii. the number and percentage of subjects experiencing an intervention-emergent AE by SOC and PT
- iii. the number and percentage of subjects experiencing an intervention-emergent AE by SOC, PT, and strongest relationship to lung transplant
- iv. the number and percentage of subjects experiencing an intervention-emergent AE by SOC, PT, and strongest relationship to EVLP
- v. the number and percentage of subjects experiencing an intervention-emergent AE by SOC, PT, and strongest relationship to ECMO
- vi. the number and percentage of subjects experiencing an intervention-emergent AE by SOC, PT, and greatest severity
- vii. the number and percentage of subjects experiencing an intervention-emergent SAE by SOC and PT
- viii. the number and percentage of subjects experiencing an intervention-emergent SAE by SOC, PT, and strongest relationship to lung transplant as determined by CEC adjudication.
- ix. the number and percentage of subjects experiencing an intervention-emergent SAE by SOC, PT, and strongest relationship to EVLP as determined by CEC adjudication.
- x. the number and percentage of subjects experiencing an intervention-emergent AE leading to death by SOC, PT, and relationship to EVLP as determined by CEC adjudication.
- xi. the number and percentage of subjects experiencing an intervention-emergent non-serious adverse event by SOC and PT
- xii. the number and percentage of subjects experiencing an intervention-emergent AE leading to study withdrawal by SOC and PT

In the overall summary of intervention-emergent AEs table (i), besides tabulating the number and percentage of subjects, the total number of intervention-emergent AE episodes will also be provided. If a subject has repeated episodes of a particular intervention-emergent AE, all episodes will be counted in the summary table.

For AE summary tables presented by SOC and PT, the table will be sorted by SOC and descending order for PT.

In the remaining summary tables, the incidence of intervention-emergent AEs will be calculated by dividing the number of subjects who have experienced the event by the total number of subjects in the FAS. Thus, the incidence of intervention-emergent AEs is shown in terms of the total number of subjects and not in terms of the total number of episodes. If a subject has repeated episodes of a particular intervention-emergent AE, only the most severe episode, or the episode with the strongest causal relationship to study intervention, will be counted in the summary tables.

A subject with more than one type of intervention-emergent AE in a particular SOC will be counted only once in the total of subjects experiencing intervention-emergent AEs in that particular SOC. Since a subject could have more than one type of intervention-emergent AE within a particular SOC, the sum of subjects experiencing different intervention-emergent AEs within the SOC could appear larger than the total number of subjects experiencing Intervention-emergent AEs in that SOC. Similarly, a subject who has experienced an intervention-emergent AE in more than one SOC will be counted only once in the total number of subjects experiencing AEs in all SOC.

All occurrences of all intervention-emergent AEs will be listed for each subject, grouped by transplant group. The listing will contain the following information: transplant group, verbatim term, SOC, PT, severity, relationship to EVLP procedure and lung transplant, date and day of onset, date and day of resolution, treatment given to treat the adverse event, the outcome, whether the event was an SAE, SAE criteria, whether it led to withdrawal, and whether it is an intervention-emergent AE. Listings will be sorted by subject identification number, onset date, SOC, and PT. If the onset date is completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates.

7.3 Clinical Laboratory Assessments

Perfusate blood gas samples will be collected hourly during the EVLP lung evaluation, both distally and proximally to the lung. Arterial blood gases (ABGs) post-transplant will be measured in order to calculate PGD grade at Baseline (Day 0, within 6 hours of admission to the ICU post-transplant) and 24, 48, and 72 hours post-transplant.

7.4 Physical Examination

A physical examination will be performed at the Baseline Visit. A by subject listing will be provided.

8. INTERIM ANALYSIS

There are no formal interim analyses planned for this study.

9. SAMPLE SIZE AND POWER CALCULATIONS

9.1 12 Month Survival

The primary endpoint for this trial has evolved with each revision of the study protocol. Originally (protocol version 1.0, dated 25 January 2018), 30-day survival was the primary endpoint with 66 EVLP subjects required. Version 2.0 of the protocol (dated 26 July 2018) modified the primary

endpoint to 6-month survival with an increase in the sample size of the EVLP group to 93. Version 3.0 of the protocol (dated 25 February 2020) modified the primary endpoint to 12-month survival, introduced the use of a Bayesian analysis, and set a performance goal that the point estimate of 12-month survival would be required to exceed 80.2%, for a decrease to the sample size of the trial with 75 EVLP subjects needed. Version 4.0 of the protocol (dated 28 January 2021) continued the use of a Bayesian analysis, and modified the performance goal to 81.2, while allowing for a sample size of the trial with 93 EVLP subjects needed.

As of the date of this approved SAP, the Sponsor has been unable to reach agreement with CDRH/FDA for the underlying justification of the performance goal nor the procedures necessary to conduct the Bayesian analysis, specifically use of Bayesian priors and weights. As such, the Sponsor convened an independent, expert panel in October 2021 to seek advice. The unanimous opinion of the panel was that the Sponsor was potentially biased by seeing the results of this open-label study and could not effectively resolve these issues without criticism. It was recommended that the Sponsor revise the primary analysis plan to an approach that mirrored that of Version 1.0 of the protocol to prevent any possible predisposition.

The sample size for this trial will remain 93 EVLP subjects but without the justification cited in the protocol for being determined by the Bayesian approach.

For transparency, a complete description of the Bayesian methodology and data simulation is specified in Appendix 11.2. This analysis will be conducted as supportive of the revised primary endpoint analysis.

9.2 Control Group

A contemporaneous Control group will be entered into this study. This Control group will provide context of the EVLP results. 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 of 75 subjects is not statistically based.

10. REFERENCES

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11. APPENDICES

11.1 Schedule of Events

Evaluation	Screening Days -365 to 0	Baseline; Day 0	Intervention Period							Follow-up
			Visit 1 (ICU); 24hr ± 4	Visit 2 (ICU); 48hr ± 8	Visit 3 (ICU); 72hr ± 12	Visit 4; Day 30 ± 5	Visit 5; Day 90 ± 10	Visit 6; 6 mon ± 14dd	Visit 7; 1 year ± 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 (lung transplant)	-	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 at rest	-	X	-	-	-	X ^e	X	X	X	(X)
ICU discharge date	-	-	-	-	(X)	(X)	-	-	-	(X)
Extubation date/time					(X)	(X)				
Hospital discharge	-	-	-	-	-	(X)	-	-	-	(X)
Hospital readmission	-	-	-	-	-	(X)	(X)	(X)	(X)	(X)
Physical capacity	-	-	-	-	-	-	X	X	X	(X)
Work status	-	-	-	-	-	-	X	X	X	(X)
Adverse event assessment	-	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Survival Assessment	-	-	-	-	-	X	X	X	X	(X)

Abbreviations: discont'n=discontinuation; FEV₁=forced expiratory volume in one second; hrs=hours; ICU=intensive care unit; I/E=inclusion/ exclusion; mon=month; PaO₂=partial pressure of oxygen in arterial blood; primary graft dysfunction; wks=weeks

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

^a Data at Baseline are 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.

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

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

^c At the time of discharge.

11.2 Sample Size Determination Using Bayesian Approach with Power Prior

The sample size for this trial was determined by the Bayesian approach with power prior [4, 5]. Given two sets of historical one-year 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, to confirm that posterior probability of 12-month survival rate greater than the performance goal of 81.2% (see Protocol Section **Error! Reference source not found.**) is at least 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 :

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

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

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

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

The sample size was determined using the simulated data from the posterior distribution. Appropriate values of hyperparameters, a and b , and the weights in the power prior, a_{01} and a_{02} , are selected based on literature [6] 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 protocol Section **Error! Reference source not found.**, and that the one-year post-transplant survival rates from the historical EVLP studies are no less than 0.825, a combination of (a, b) with mean of the Beta prior distribution (hyper-mean) no less than 0.812 is a reasonable estimate (see Table A3). The difference of one-year 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 A2 displays the sample sizes required for expected performance goal varying from 0.792 to 0.812 with various weights and parameter combinations. The sample size of 93 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 one-year	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: - Device used - Personnel - Perfusion procedure - Transplant centers - Recipient criteria - Donor/donor lung exclusion criteria - Donor/donor lung inclusion criteria	- Identical device - Same personnel - Same EVLP facility and perfusion procedures 7 common transplant centers - 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) - Donor lung exclusion criteria identical - Donor inclusion criteria: 44% of subjects enrolled with identical criteria to Pivotal. 56% enrolled with 95% similar criteria.	95% identical device. - LBE personnel trained by Toronto Team - Different facility, same procedures. - Toronto data based on single-center experience vs multi-center trial. - Inclusion/Exclusion 80% similar - Donor exclusion criteria 90% similar - 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

Performanc e Goal	n	a01	a02	a	b	hyper- mean	hyper- sd	power	Type I error
81.2%	93	0.6	0.2	34	8	0.810	0.060	0.80	0.086
81.2%	93	0.5	0.2	33	7	0.825	0.059	0.80	0.086
81.2%	93	0.5	0.2	29	6	0.829	0.063	0.80	0.086
81.2%	93	0.5	0.2	34	7	0.829	0.058	0.80	0.086
80.2%	75	0.6	0.2	37	9	0.804	0.058	0.82	0.096
80.2%	75	0.5	0.2	42	10	0.808	0.054	0.82	0.096
80.2%	75	0.6	0.2	42	10	0.808	0.054	0.82	0.096
80.2%	75	0.5	0.2	34	8	0.810	0.060	0.82	0.096
80.2%	75	0.6	0.2	43	10	0.811	0.053	0.82	0.096
80.2%	75	0.5	0.2	44	10	0.815	0.052	0.82	0.096
79.2%	60	0.5	0.2	40	10	0.800	0.056	0.81	0.095
79.2%	60	0.5	0.2	36	9	0.800	0.059	0.81	0.095

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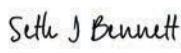
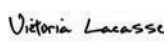
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