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A Phase 2, Multicenter, Open-Label Study to Measure the Safety of Extending Preservation and Assessment Time of Donor Lungs Using Normothermic Ex Vivo Lung Perfusion and Ventilation (EVLP) as Administered by the Sponsor Using the Toronto EVLP System

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STATISTICAL ANALYSIS PLAN

Version 2.0

Document Date 08 JAN 2020

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STATISTICAL ANALYSIS PLAN
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SAP Revisions

Version 1.0 of the SAP was finalized at the time of Protocol version 5.0 (02MAY2016). The following table details the changes made to the SAP following subsequent protocol amendments. These changes may or may not be due to the protocol amendments.

Protocol Version # Date	SAP Section	Modification	Description and Rationale
6.0 03NOV2019		Updated approval page to new author and sponsor approvers.	NA
6.0 03NOV2019	3.1	Minor wording changes	NA
6.0 03NOV2019	4	Removed: A one-sided 95.0% CI will be provided, as appropriate, for the primary endpoints, and two sided 95.0% CI will be presented for all endpoints, as appropriate. Minor wording changes	This statement was removed since it was determined confidence intervals would not be needed for all efficacy endpoints.
6.0 03NOV2019	5.3.1	Added: ABO blood group, "A" blood group subtype, Rh factor	This data was collected and will be summarized for recipients.
6.0 03NOV2019	5.3.2	Added: ABO blood group, "A" blood group subtype, Rh factor	This data was collected and will be summarized for donors.
6.0 03NOV2019	5.3.4	Removed: Donor and recipient ABO blood group, "A" blood group subtype, Rh factor Added: Donor and recipient ABO blood group match	The data is summarized for recipients alone and donors alone in the sections above. The cross match was added as useful transplant information to summarize.
6.0 03NOV2019	5.5	Added: at each visit Added: The use of concomitant medications in the 2 weeks leading up to the onset of a serious adverse event (SAE) will be summarized. The number and percent of FAS subjects using each concomitant medication in that period prior to a SAE will be tabulated by Anatomical, Therapeutic, and Chemical (ATC) class, and by preferred name, transplant subtype and overall.	Specifying the collection of concomitant medications at each visit. Specifying the summary of concomitant medications taken in the 2 weeks preceding an SAE.

Protocol Version # Date	SAP Section	Modification	Description and Rationale
6.0 03NOV2019	6	Changed: "Efficacy" to "Effectiveness"	NA
6.0 03NOV2019	6.1	Removed reference to one-sided 95% CIs being calculated	It was determined that the two-sided 95% CIs would provide the most complete and useful summary information.
6.0 03NOV2019	6.2	Removed: "along with two sided 95% CIs"	Confidence intervals were determined not to be needed and that the summary statistics for each group will provide enough information for the secondary endpoints of this trial.
6.0 03NOV2019	6.3	Added: ", the number of re-hospitalizations per subject, and whether the subject had a re-hospitalization related to transplant." Removed: "along with two sided 95% CIs" Removed: "Change from baseline values will be calculated and provided for FEV_1."	This data was collected and will be summarized. Confidence intervals were determined not to be needed and that the summary statistics for each group will provide enough information for the exploratory endpoints of this trial. FEV_1 values summarized at each visit were deemed sufficient for this exploratory endpoint.
6.0 03NOV2019	7.2.5	Added: "the number and percentage of subjects experiencing an intervention-emergent AE by strongest relationship to lung transplant" Removed: "the number and percentage of subjects experiencing an intervention-emergent AE by action taken" Added: "the number and percentage of subjects experiencing an intervention-emergent AE by SOC and PT"	This summary was deemed necessary. This summary was deemed not necessary. This summary was deemed necessary.

Protocol Version # Date	SAP Section	Modification	Description and Rationale
6.0 03NOV2019	7.3	Removed: "Perfusate blood gas will be collected hourly during the EVLP lung evaluation, both distally and proximally to the lung."	These data were not collected in the EDC and are not relevant to the SAP.
6.0 03NOV2019	8	Minor wording changes Added: "This report was submitted to FDA on 26 July 2017. The Agency determined the safety data were sufficient to allow enrollment to continue on 25 August 2017."	NA Added to provide complete information following the submission of the report to FDA and agency response.
6.0 03NOV2019	10.1	Removed: Schedule of Events: Long-term Follow-up	This is not relevant to the SAP.

Table of Contents

1. INTRODUCTION

This document details the Statistical Analysis Plan for study Protocol PXUS 14-001, v5.0, a phase 2, multicenter, open-label study to measure the safety of extending preservation and assessment time of donor lungs using normothermic ex vivo lung perfusion and ventilation (EVLP) as administered by the sponsor using the Toronto EVLP system.

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 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 20% of brain dead donors who are used for transplanting other solid organs. The described reason for declining the majority of the available donor lungs by transplant programs has been listed as being due to "Poor Organ Function" and "No Recipient Found."

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, or additional time was available to meet the complex logistical demands of procurement and transplantation. Introduction of technologies, such as *Ex vivo* Lung Perfusion (EVLP), might facilitate more in-depth assessment of lung condition, thereby enabling transplant programs to use lungs for transplant that are currently discarded. The Toronto EVLP System (TES) was demonstrated as technically feasible and safe, permitting perfusion of donor lungs for up to 6 hours (hrs) in clinical practice (and 18 hrs in the research setting). By permitting a longer preservation period, TES extended the time available for assessment of donor lungs under near-physiologic conditions. The traditional feasibility study will generate preliminary safety and effectiveness information, evaluating the TES at a central facility for extended donor lung preservation. This information may be used to plan an appropriate future pivotal study, as part of efforts to inform further development.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of this study is to evaluate the short-term safety of subjects receiving a lung transplant, where the lung(s) was perfused by the Sponsor using the Toronto EVLP System (TES). Assessment of Primary Graft Dysfunction (PGD) Grade 3 at 72 hours post-transplant (T72) and 30-day mortality will represent the outcome measures, and the primary endpoints are the following two measures:

- The proportion of recipients with PGD Grade 3 (PGD3) assessed at T72
- 30-day mortality post-transplant

2.1.2 Secondary Objective

The secondary objective of this study is to evaluate the short-term safety of subjects receiving a lung transplant where the lung(s) has been perfused via the TES performed by the Sponsor by

assessment of the following:

- PGD Score (Grades 0-3) measured at 0, 24, 48, and 72 hours post-transplant
- Time to first extubation (hours)
- 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 prior to discharge post-transplant
- Total preservation time (TPT), defined as the elapsed time between first allograft lung removal from cold storage time prior to transplant in the recipient and the donor aortic cross clamp time at procurement
- Assessment of the overall safety of TES lung transplants during subject's participation in the study, as reported through adverse events (AEs)

2.1.3 Other Objectives

Additional objectives of this study include evaluation of intermediate and longer-term safety and preliminary efficacy in subjects receiving a lung transplant where the lung(s) was perfused using the TES performed by the Sponsor. Assessments will include the following:

- Initial ICU partial pressure of oxygen in arterial blood (PaO_2): Evaluated as first PaO_2 measured after ICU admission.
- Forced Expiratory Volume in one second (FEV_1) evaluated at time of discharge, 30 days, 90 days, 6 months and 1 year post-transplant. FEV_1 is measured as a percentage of predicted normal value.
- Oxygen requirement at rest evaluated at time of discharge, 30 days, 90 days, 6 months and 1 year post-transplant. Oxygen required at rest is measured in liters per minute (L/min).
- Subject survival evaluated at 90 days, 6 months, and 1 year post-transplant. Measured as living or dead. If the subject expires within first year post-transplant, the date of death and primary cause of death will be collected.
- Graft survival evaluated at 30 days, 90 days, 6 months, and 1 year post-transplant. Measured as functioning or failed. If the graft fails within first year post-transplant, the date of graft failure will be collected.
- Primary cause of graft failure evaluated at 30 days, 90 days, 6 months, and 1 year post-transplant on all failed grafts.
- Bronchiolitis Obliterans Syndrome (BOS) Grade evaluated at 90 days, 6 months, and 1 year post-transplant.
- Number of re-hospitalizations after transplant evaluated at 6 months and 1 year post-transplant. Measured as total number of hospitalizations since initial discharge.
- Physical capacity evaluated at 90 days, 6 months, and 1 year post-transplant.

- Working for income after transplant evaluated at 90 days, 6 months, and 1 year post-transplant.

The above information will also be collected on subjects enrolled in a contemporaneous control group to provide context for EVLP results and to inform control measures for future research.

2.2 Endpoints

2.2.1 Primary Endpoints

The primary endpoints of the study are PGD3 Score at 72 hrs post-transplant (T72) and 30-day mortality.

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.

2.2.2 Secondary Endpoints

Secondary endpoints include the following:

- PGD Score (Grades 0-3) measured at 0, 24, 48, and 72 hours post-transplant
- Time to first extubation
- ICU 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 prior to discharge post-transplant
- TPT defined as the elapsed time between first allograft lung removal from cold storage time prior to transplant in the recipient and the donor aortic cross clamp time at procurement
- Assessment of the overall safety of TES lung transplants during subject's participation in the study, as reported through AEs

2.2.3 Exploratory Endpoints

Other safety endpoints that will be analyzed include:

- Initial ICU PaO_2: Evaluated as first PaO_2 measured after ICU admission.
- FEV_1: Evaluated at time of discharge, 30 days, 90 days, 6 months, and 1 year post-transplant. FEV_1 is measured as a percentage of predicted normal value.
- Oxygen Requirement at Rest: Evaluated at time of discharge, 30 days, 90 days, 6 months, and 1-year post-transplant.
- Subject Survival: Evaluated at 90 days, 6 months, and 1 year post-transplant. Measured as living or dead. If the subject expires within first year post-transplant, the date of death and primary cause of death will be collected.
- Graft Survival: Evaluated at 30 days, 90 days, 6 months, and 1 year post-transplant. Measured as functioning or failed. If the graft fails within first year post-transplant, the

date of graft failure will be collected.

- Primary Cause of Graft Failure: Evaluated at 30 days, 90 days, 6 months, and 1 year post-transplant on all failed grafts.
- Bronchiolitis Obliterans Syndrome (BOS) Grade: Evaluated at 90 days, 6 months, and 1 year post-transplant.
- Number of Re-hospitalizations after Transplant: Evaluated at 6 months and 1 year post-transplant. Measured as total number of hospitalizations since initial discharge.
- Physical Capacity: Evaluated at 90 days, 6 months, and 1 year post-transplant.
- Working for Income after Transplant: Evaluated at 90 days, 6 months, and 1 year post-transplant.

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is an unblinded, non-randomized, traditional feasibility study to evaluate the safety of subjects undergoing lung transplant using lungs after EVLP, and performed exclusively by the Sponsor at the Sponsor's facility using the Toronto EVLP System (TES). For details on inclusion/exclusion criteria, please refer to the study protocol PXUS 14-001. A schedule of study assessments can be found in Appendix A of this document.

Once the donor lung is accepted following EVLP, the eligible recipient, who has provided written informed consent, and receives the lung transplant, is enrolled into the study. Subjects who consent for the current EVLP study (PXUS 14-001) but receive a conventional (i.e. non-EVLP) lung transplant will be considered for a contemporaneous control group matched to the EVLP treatment group. This matching will take on a subject-by-subject basis and only after an EVLP subject has been enrolled at that Study Center. Investigators and their team will be notified by the Sponsor on a real-time basis of the specific matching criteria required for a control subject as EVLP subjects are enrolled. In order to be considered for eligibility, the control subject must "match" a priori to at least one EVLP subject who has already been enrolled at that Study Center based on the following criteria: single-lung transplant (SLT) versus double-lung transplant (DLT) and Lung Allocation Score Disease Diagnosis Group (LASDDG).

A sample size of 132 subjects, receiving either SLT or DLT, is planned for this study, where 66 subjects receive donor lung(s) after EVLP (EVLP Group) and 66 subjects are in a contemporaneous control group (Control Group). No more than two-thirds of the subjects who are enrolled (44 subjects per group) will have received a SLT or DLT. The post-intervention phase of the study will then be split into two phases: 1) the Analysis Phase, which includes follow-up within one year post-intervention and 2) Long-term Follow-up, which will capture outcome data annually from 1-year post-intervention until 5-years post-intervention. Although the study will continue after one year, the database will be locked for analyses of endpoints after the last subject has his/her study visit at 1 year. The Long-term Follow-up data will be summarized when the study has completed in support of long-term evaluation.

Analysis Phase

Following transplantation, subjects will be admitted to the ICU, and initial PaO_2 and PGD Score

will be recorded. The subject's PGD Score will be recorded every 24 hrs for the next 72 hrs. The ICU discharge date will be documented. Study visits will occur 30 days (±5), 90 days (±10), 6 months (±2 weeks), and 1 year (±4 weeks) post-transplant. Study assessments will be performed as outlined in the Schedule of Events.

Long-term Follow-Up

Although the database will be locked and analyses of endpoints performed after the last subject has his/her study visit at 1 year, the Sponsor will continue to collect specified outcome parameters that are required to be reported by transplant centers to OPTN/United Network for Organ Sharing (UNOS). Collection will be annually for 5 years post-intervention.

3.2 Treatment

EVLP is a novel technology that allows extended assessment of lungs whose suitability for transplantation is initially uncertain. By protocol design, EVLP-treated lungs undergo a longer period of total preservation, including an initial cold ischemic time (CIT-1), a period of normothermic EVLP assessment, and a final round of CIT (CIT-2). The extended donor lung preservation time may enable better logistical coordination of the recipient and donor hospital transplant teams.

Upon retrieval, donor lungs will be packaged and transported to the Sponsor's EVLP facility. The EVLP procedure will be performed by specifically-trained *Ex Vivo* Lung Specialists under remote video supervision by one of the Sponsor's Expert Medical Consultants. The Sponsor will perfuse the lung using the TES for up to 6 hours, collecting and relaying lung function assessment data hourly, or as requested by the Study Center Investigator/team. Additionally, the Study Center surgeon 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.

The Study Center Investigator/team, together with the Sponsor's Expert Medical Consultants, will monitor the donor lung(s) for EVLP inclusion criteria and collaborate to determine the timing of EVLP termination. However, final decisions reside with the Study Center Investigator/team. Upon acceptance of an EVLP donor lung by the Study Center, the single lung or lung block is cooled according to TES methodology to 10°C, and perfusion and ventilation are stopped. This point marks the start of CIT-2. The end of CIT-2 is defined as the time the organ is removed from cold storage to begin the implantation phase of the transplantation procedure. The time between the organ's removal from cold storage to reperfusion in the recipient is known as warm ischemic time (WIT). Total preservation time for the first lung transplanted from donor lung retrieval to the end of CIT-2 must not be greater than a combined 22 hrs and individual phase limits as follows:

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

Total preservation time for the second lung transplanted from donor lung retrieval to the end of CIT-2 must not be greater than a combined 26 hrs and 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 Randomization Scheme and Treatment Arm Assignment

This is an open-label study and no randomization will apply. Subjects 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 selected to best match the EVLP group with respect to the following criteria: SLT/DLT, and Lung Allocation Score Disease Diagnosis Group (LASDDG). 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 Immunodeficient Disorders
- Group D: Restrictive Lung Disease

The goal is to provide a control group with similar characteristics and risk as the experimental group receiving EVLP.

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 one year post-transplant for the Analysis Phase. In addition, outcome data will be collected annually up to 5 years post-transplant. The study duration for the Analysis Phase (from first patient, first visit [FPFV] to last patient, last visit [LPLV] prior to database lock) is expected to be 3 years. The estimated time to complete enrollment is approximately 24 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 regiments. 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

No statistical hypotheses will be tested in this study. Rather, displays of study results – regarding intervention-related safety among the transplant groups (EVLP or Control) – will primarily utilize descriptive statistics, as noted below.

Unless otherwise specified, continuous variables will be summarized by presenting the number of non-missing observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by presenting the number of subjects and percentage for each category.

Summary results will be provided for each transplant group. All tabulations will be based on pooled data across centers. Analyses will be performed primarily on data collected during the Analysis Phase (1-year post-intervention). The database will be locked for analysis of endpoints after the last subject completes his/her study visit at Year 1, and all queries have been resolved. The Long-term Follow-up data will be summarized when the study has completed in support of

long-term evaluation.

Analyses will be performed using SAS for Windows statistical software, version 9.2 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 statistical analyses.

Subject data will be listed, sorted by transplant group and subject number.

4.1 Data Quality Assurance

Lung Bioengineering, or its designated representative, will conduct a Site Initiation Visit (SIV) for each study site to verify the qualifications of the investigator, become familiarized with site staff assigned to the study, and inform the investigator of responsibilities and procedures for ensuring correct study documentation.

The clinical investigator will be required to prepare and maintain adequate and accurate case report forms (CRFs), which are designed to include all observations and other data pertinent to the study for each study participant. All information recorded on the CRFs for this study must be consistent with the investigator's source documentation for the study participants.

A study coordinator at the investigative site will enter patient data into a remote data capture database (RDC) by completing electronic case report forms (eCRFs). All information recorded in the eCRFs for this study must be consistent with the investigator's source documentation for the study participants. The investigative site will make available source documents to CTI personnel monitoring the study. The study monitor will verify consent of all subjects to participate in the study and will perform 100% source document verification of the eCRF data. The only exception is that the donor and EVLP information arriving with the corresponding lungs will be entered into the EDC System by designated Sponsor staff, with a copy of the source being maintained at the Sponsor facility and original source forwarded to the recipient transplant center if applicable.

A CTI Clinical Data Associate (CDA) will review the data for discrepancies via programmed electronic consistency checks, data listings, or manually. Any discrepancies discovered via the data review process will be issued as queries in the RDC system to the investigative site for resolution. 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 analysis.

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

All SAS programs used to create analysis datasets and output will be validated by ensuring that the ".log" files are void of all errors, warnings and notes indicative of problems. Additionally, each program will be checked to ensure that it performs according to the program specification. All programs are developed and validated by separate members of the CTI Biostatistics Department.

When performing a quality control (QC) review of listings and tables output from SAS, it is not always possible to perform a 100% QC review of all fields. If a 100% QC review is not to be performed, the sample size of fields to undergo QC review may be determined by utilizing American National Standards Institute (ANSI) sampling procedures. Sampling procedures are conducted using "normal" inspection criteria (Inspection Level II, Single, and Normal) and an

Acceptable Quality Level (AQL) of 0.010%. The following shows the sampling criteria:

Single Normal sampling procedure for Acceptable Quality Level (AQL) 0.010%

Number of Fields	Sample Size	Accept/Reject Criteria
2-8	2	0/1
9-15	3	0/1
16-25	5	0/1
26-50	8	0/1
51-90	13	0/1
91-150	20	0/1
151-280	32	0/1
281-500	50	0/1
501-1,200	80	0/1
1,201-3,200	125	0/1
3,201-10,000	200	0/1
10,001-35,000	315	0/1
35,001-150,000	500	0/1
150,001-500,000	800	0/1
500,001-up	1,250	0/1

4.2 Analysis Sets

The full analysis set (FAS) is defined as all enrolled subjects. All efficacy and safety analyses will be performed on the FAS.

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 safety analysis is the proportion of subjects with a PDG3 at T72. PGD is measured in all lung transplant subjects at specific intervals following transplantation, including 24, 48, and 72 hrs. Protocol training will focus on the importance of obtaining PGD at T72 in every study

subject.

If a subject dies prior to T72 measurement, they will be counted as a "failure" and classified as PGD3 for the primary safety analysis. If the T72 value is missing (not collected, not reported, not properly documented), then PGD3 will be assumed ("failure"), and they will be classified as such for the primary safety analysis. Missing data in other safety analyses will remain missing.

4.5 Multiple Comparisons

No multiple comparisons are planned for this study.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

A table of counts of subjects in the FAS will be provided. Reasons for not completing study as planned and reasons for premature withdrawal will be tabulated for the groups.

5.2 Protocol Deviations

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

5.3 Demographic and Baseline Characteristics

Demographic data and baseline characteristics for all FAS 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.

5.3.1 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) and height (cm)
- ABO blood group, "A" blood group subtype, Rh factor
- LAS Disease Diagnosis Group
- Lung Allocation Score at time of waitlist addition and at time of lung match

5.3.2 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)
- ABO blood group, "A" blood group subtype, Rh factor
- Primary cause, mechanism, and circumstances of death

5.3.3 EVLP Information

- Lungs received (single right, single left, bilateral)
- EVLP time (hours)
- Donor lung evaluation (met transplant inclusion criteria, accepted for transplant)
- Organs shipped

5.3.4 Procurement Information

- Donor type
- Donor and recipient ABO blood group match
- Lung type
- Lung inclusion criteria met
- Ventilation parameters (terminal PaO_2, tidal volume, FiO_2, PEEP, rate)
- Procurement information (Flush solution, flush type, vasodilator, antegrade volume, retrograde volume)

5.4 Medical History

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 PT. The data will also be listed.

5.5 Prior and Concomitant Medications

Concomitant medications will be coded using World Health Organization (WHO) drug classifications. The number and percent of FAS subjects using concomitant medications at each visit will be tabulated by Anatomical, Therapeutic, and Chemical (ATC) class, and by preferred name, transplant subtype and overall.

The use of concomitant medications in the 2 weeks leading up to the onset of a serious adverse event (SAE) will be summarized. The number and percent of FAS subjects using each concomitant medication in that period prior to a SAE will be tabulated by Anatomical, Therapeutic, and Chemical (ATC) class, and by preferred name, transplant subtype and overall.

6. EFFECTIVENESS ANALYSIS

The study endpoints are safety related and therefore there will be no effectiveness analyses.

6.1 Primary Endpoints and Analysis

Primary Graft Dysfunction Score

The PGD3 Score at 72 hours post-transplant (T72) will be used as the basis for the primary safety endpoint for analysis. The primary endpoint (PGD3 T72) will be calculated from PGD T72 as follow: PGD T72 = {0, 1, & 2} will be coded to PGD3 T72 = 0 and PGD T72 = {3} will be coded

to PGD3 T72 = 1.

If a subject dies prior to the T72 measurement, they will be coded to PGD3 T72 = 1. If the T72 value is missing (not collected, not reported, not properly documented), then PGD3 will be coded to PGD3 T72 = 1 for the primary safety analysis.

The subject's PGD Score is to be determined by the Investigator at Baseline (Day 0) after transplantation and upon admission to the ICU, as well as 24, 48, and 72 hours post-transplant.

The primary analysis will be descriptive. The proportion of subjects with PGD3 T72 by Transplant Group (EVLP and Control) will be presented along with a two-sided 95% CI.

There will be no inferential testing conducted.

30-Day Mortality

Subject survival, measured as living or dead, will be recorded for Day 30, Month 6, and Year 1 post-transplant. The primary endpoint of 30-Day mortality will be derived as follows: Living at Day 30 will be coded to 0, and Dead before or on Day 30 will be coded to 1. If the vital status of the subject is missing (not collected, not reported, not properly documented), then 30-Day Mortality will remain missing for the primary analysis.

The primary analysis will be descriptive. The proportion of subjects with 30-Day Mortality by Transplant Group (EVLP and Control) will be presented along with a two-sided 95% CI.

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. There will be no inferential testing conducted.

6.2 Secondary Endpoints and Analyses

Secondary endpoints include the following:

- PGD Score (Grades 0-3) measured at 0, 24, 48 and 72 hours post-transplant
- Time to first extubation (hours)
- ICU 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 prior to discharge post-transplant
- TPT defined as the elapsed time between first allograft lung removal from cold storage time prior to transplant in the recipient and the donor aortic cross clamp time at procurement
- Assessment of the overall safety of TES lung transplants during subject's participation in the study, as reported through AEs.

The secondary endpoints of PGD score will be summarized by presenting the number of subjects and percentage for each category. All other secondary endpoints are continuous and will be presented using descriptive statistics by Transplant Group. Other supportive endpoints may be provided to supplement the secondary analyses. Analysis of the overall safety of TES lung transplants is detailed in Section 7.2.5.

Results may be displayed graphically. There will be no inferential testing conducted.

6.3 Exploratory Endpoints and Analyses

Other safety endpoints that will be analyzed include:

- Initial ICU PaO_2: Evaluated as first PaO_2 measured after ICU admission.
- FEV_1: Evaluated at time of discharge, 30 days, 90 days, 6 months and 1 year post-transplant. FEV_1 is measured as a percentage of predicted normal value. Oxygen Requirement at Rest: Evaluated at time of discharge, 30 days, 90 days, 6 months and 1 year post-transplant.
- Subject Survival: Evaluated at 90 days, 6 months and 1 year post-transplant. Measured as living or dead. If the subject expires within first year post-transplant, the date of death and primary cause of death will be collected.
- Graft Survival: Evaluated at 30 days, 90 days, 6 months and 1 year post-transplant. Measured as functioning or failed. If the graft fails within first year post-transplant, the date of graft failure will be collected.
- Primary Cause of Graft Failure: Evaluated at 30 days, 90 days, 6 months and 1 year posttransplant on all failed grafts.
- Bronchiolitis Obliterans Syndrome (BOS) Grade: Evaluated at 90 days 6 months and 1 year post-transplant.
- Number of Re-hospitalizations after Transplant: Evaluated at 6 months and 1 year post-transplant. Measured as total number of hospitalizations since initial discharge, the number of re-hospitalizations per subject, and whether the subject had a re-hospitalization related to transplant.
- Physical Capacity: Evaluated at 90 days, 6 months and 1 year post-transplant.
- Working for Income after Transplant: Evaluated at 90 days, 6 months and 1 year post-transplant.

Initial ICU PaO_2 and FEV_1 will be presented using descriptive statistics by Transplant Group. All other exploratory endpoints are categorical and will be summarized by presenting the number of subjects and percentage for each category. Other supportive endpoints may be included as needed.

Results may be displayed graphically. There will be no inferential testing conducted.

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

7. SAFETY ANALYSIS

Safety analyses to be performed include: adverse events, physical examination, and vital signs.

7.1 Extent of Exposure

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

7.2 Adverse Events

Adverse events will be recorded throughout the study, but only those occurring within the first 90 days post-transplant will be reported to the Sponsor, unless they are considered SAEs. All SAEs will be recorded and reported to the Sponsor throughout the Analysis Phase. Adverse events 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, which 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, 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.

7.2.4 Serious Adverse Events

A serious adverse event (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 for the FAS:

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 greatest severity
   c. the number and percentage of subjects experiencing an intervention-emergent AE by strongest relationship to lung transplant
   d. the number and percentage of subjects experiencing an intervention-emergent AE by strongest relationship to study intervention
   e. the number and percentage of subjects experiencing an Intervention-emergent SAE

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 study intervention

iv. the number and percentage of subjects experiencing an intervention-emergent AE by SOC, PT, and greatest severity

v. the number and percentage of subjects experiencing an intervention-emergent SAE by SOC and PT

vi. 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.

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 SOCs.

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 study intervention, 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, 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

Arterial blood gases (ABGs) post-transplant will be measured in order to calculate PGD grade at Baseline (Day 0 within 24 hours of transplant), 24, 48, and 72 hours post-transplant.

Any clinically significant abnormal laboratory result from Day-0, post-transplant and per protocol is not considered an anticipated adverse event not related to EVLP, is to be recorded as an AE and tabulation of those events will occur within AE summaries.

7.4 Vital Signs

Assessments of vital signs are to be collected at each scheduled study visit. The following vital sign parameters should be recorded: height (baseline only), weight, heart rate, blood pressure, respiration rate, and oxygen saturation. Descriptive summaries of the vital sign parameters (both raw and change from baseline values) will be prepared for each transplant group by visit. Vital sign data will also be listed for each subject. Clinically significant abnormal values will be flagged.

Any clinically significant abnormality prior to enrollment is to be recorded as medical history, and tabulation of those events will occur within medical history summaries. Any clinically significant abnormal change from baseline post-transplant is to be recorded as an AE and tabulation of those events will occur within AE summaries.

7.5 Physical Examination

A physical examination will be performed at the Baseline Visit. Symptom-directed physical examinations will be performed again at Day 30 and Month 6 post-transplant. Any values judged by the Investigator to be clinically significant abnormal changes from Baseline (before study intervention) will be recorded as an AE. A listing of abnormalities will be provided.

8. INTERIM ANALYSIS

There are no formal interim analyses planned for this study. However, the Sponsor was required to temporarily pause the study at EVLP subject #20 to allow time for the FDA to review safety data on the first 10 EVLP and any control subjects enrolled who reach 90 days post-transplant. This report was submitted to FDA on 26 July 2017. The Agency determined the safety data were sufficient to allow enrollment to continue on 25 August 2017.

9. SAMPLE SIZE AND POWER CALCULATIONS

In order to provide a sufficient number of subjects for reliable estimation of the primary endpoints, sample size was calculated based on a primary endpoint of PGD3 at T72. Estimates of PGD3 at T72 were based on historical data from EVLP transplant studies where EVLP subjects had rates of PGD3 at T72 ranging from 0% to 15% and conventional transplant subjects ranging from 16.8% to 30%. Assuming a PGD3 at T72 of 10% and a one-sided 95.0% confidence interval (CI) for a single proportion using the large sample normal approximation adjusted for a finite population of size 2057 (number of lung transplants performed in the US in 2015), 66 subjects will be needed for the expected upper bound of the CI to not exceed a rate of 16%. A total of 66 EVLP subjects and 66 Control subjects will be included in this study.

Rates of 30-day mortality in the EVLP transplant studies have been low, ranging from 3% to 4%. For a sample size of 66, the probability of observing at least one event will be approximately 87% to 93% if the true probability of 30-day mortality is 3% to 4%. Subjects will be entered into the study as EVLP transplants occur; however, enrollment to either transplant subtype (single-lung, double-lung) will be limited to 44 subjects to provide a reasonable number of subjects of both subtypes for subgroup examinations.

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 66 subjects, and subjects will be matched to the EVLP Group for similarity. Because the ratio of standard lung transplant to EVLP transplant is estimated to be approximately 4:1, it is feasible to obtain a control-EVLP match within the anticipated duration of the study.

10. APPENDICES

10.1 Appendix A: Schedule of Events

Schedule of Events Within 1 Year Post-Intervention

Evaluation	Screening Days -365 to 0	Baseline; Day 0	Post-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 ± 2wks	Visit 7; 1 year ± 4 wks	Premature Discont'n
Signed Informed Consent[b]	X	X	-	-	-	-	-	-	-	-
I/E Criteria	X	X[a]	-	-	-	-	-	-	-	-
Print conmeds source		X[a]	-	-	-	X	-	-	X	-
Donor data collection[c] (Sponsor responsibility)	-	X	-	-	-	-	-	-	-	-
EVLP data collection[d] (Sponsor responsibility)	-	X	-	-	-	-	-	-	-	-
Demographics and Baseline Disease Characteristics	X	X[a]	-	-	-	-	-	-	-	-
Medical History	X	X[a]	-	-	-	-	-	-	-	-
Study intervention (lung transplant)	-	X	-	-	-	-	-	-	-	-
Post-transplant Assessments (Study Investigator)										
Vital sign assessments	X	X	X	X	X	X	X	X	X	X
Physical Examination	-	X[a]	-	-	-	X	-	X	-	-
PGD Score (Section 6.7)	-	X	X	X	X	-	-	-	-	-
PaO_2 and FiO_2	-	X	-	-	-	-	-	-	-	-
Pulmonary function tests						X[e]	X	X	X	(X)
FEV_1	-	-	-	-	-	X[e]	X	X	X	(X)
Oxygen at rest	-	-	-	-	-	X[e]	X	X	X	(X)
BOS Grade	-	-	-	-	-	-	X	X	X	(X)
ICU discharge	-	-	-	-	(X)	(X)	-	-	-	(X)
Extubation date/time					(X)	(X)				
Hospital discharge	-	-	-	-	-	(X)	-	-	-	(X)
Hospital redadmission	-	-	-	-	-	(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)

Graft Survival Assessment	-	-	-	-	-	X	X	X	X	(X)
Survival Assessment	-	-	-	-	-	X	X	X	X	(X)

Abbreviations: BOS=bronchiolitis obliterans syndrome; conmed=concomitant mediations; discont'n=discontinuation; FEV_1=forced expiratory volume in one minute; hrs=hours; ICU=intensive care unit; I/E=inclusion/exclusion; mon=month; PaO_2=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 must be 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 10.4.1).

[c] Collection of donor demographics and suitability data. Confirm donor lung inclusion/exclusion criteria (Section 5.2.1 and Section 5.2.2).

[d] Collect EVLP case data to determine transplant suitability and lung inclusion/exclusion criteria (Section 5.2.3).

[e] At the time of discharge.