STATISTICAL ANALYSIS PLAN

Protocol OCS-LVR-092014

International Randomized Trial to Evaluate the Effectiveness of the Portable Organ Care System (OCS™) Liver for Preserving and Assessing Donor Livers for Transplantation (OCS Liver PROTECT Trial)

January 30, 2020
Version 2.0

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Sponsor: TransMedics, Inc.

Study Number: OCS-LVR-092014

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

Term	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AT	As Treated Population
BMI	Body Mass Index
CEC	Clinical Events Committee
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
DBD	Donor after Brain Death
DCD	Donor after Circulatory Death
EAD	Early liver Allograft Dysfunction
GGT	Gamma-Glutamyl Transferase
ICU	Intensive Care Unit
INR	International Normalized Ratio
IWRS	Interactive Web Response System
LLT	Lowest Level Term
LGRSAE	Lung Graft Related Serious Adverse Event
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
MI	Multiple Imputation
mITT	Modified Intent-to-Treat Population
OCS	Organ Care System
PP	Per-Protocol Population
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard of Care
TEAE	Treatment-Emergent Adverse Event

1. INTRODUCTION

Descriptions of planned analyses are provided in order to avoid post hoc decisions that may affect the interpretation of the statistical analysis. The statistical methods applied in the design and planned analyses of this study are consistent with the International Conference on Harmonisation (ICH) guideline *Statistical Principles for Clinical Trials* (1998).

This Statistical Analysis Plan (SAP) will be finalized prior to data analysis (and before database lock). Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR.

2. STUDY OBJECTIVE

The objective of this trial is to compare the safety and effectiveness of the OCS™ Liver (OCS) vs. standard cold storage (Control) to preserve and assess donor livers having one or more of the following characteristics:

- Donor age ≥ 40 years old
- Expected cross clamp time ≥ 6 hours
- Donor after circulatory death (DCD) with age ≤ 55 years old
- Steatotic liver >0% and ≤40% macrosteatosis at time of retrieval (based on retrieval biopsy readout only if the donor liver was clinically suspected to be fatty by the retrieval surgeon at time of liver retrieval)

3. STUDY DESIGN

3.1. Overview

This study is a prospective, multi-center, randomized, controlled Phased Pivotal trial with transplanted recipients assigned to either the OCS Liver arm (OCS - treatment) or standard of care cold storage arm (SOC - control). The trial will have two parts (Part A rolling into large Part B, assuming stopping rule is not triggered):

- Part A: Include the first 20 randomized transplanted liver recipients with pre-specified stopping rule to ensure safety.
- Part B: assuming no stopping rule was triggered, the trial enrollment will continue beyond the initial 20 transplanted recipients in Part A into Part B, while the data from the first 20 subjects are being reviewed. All of the final analyses of the study will be based on the pooled data from Parts A and B.

This trial will be conducted at no more than 25 institutions in the United States and worldwide (Europe, Australia and Canada) and will include up to 300 transplanted Liver recipients. The number of subjects was determined as described in Section 3.4 of this statistical analysis plan. All subjects will be followed for a minimum of 30 days post-transplant. Patients will be followed for a maximum of 24 months from the date of transplantation. The summary of the follow-up is as follows:

- All subjects will be followed from transplant to discharge
- Thirty-day patient and graft survival will be documented on Day 30 post-transplant eCRF
- 6, 12, and 24 months patient follow-up.

3.2. Method of Assigning Subjects to Treatment

After confirmation of eligibility, obtaining informed consent, and a matching donor liver is identified, potential liver transplant recipients will be randomized 1:1 to have their donor livers preserved using either the OCS Liver perfusion or the standard cold storage preservation technique using cold flush and storage. Randomization will be performed through the Interactive Web Response System (IWRS). Subjects who are not transplanted with the matching donor liver will be re-randomized and treated as a new subjects without any randomization assignment.

3.3. Blinding

Not applicable.

3.4. Determination of Sample Size

The sample size for this trial was determined based on the primary effectiveness endpoint, Early Liver Allograft Dysfunction (EAD) in the first 7 days post-transplantation. The sample size calculation assumed a one-sided, normal approximation test for non-inferiority, an alpha level of 0.05, a non-inferiority margin of 0.075, a 1:1 allocation, true proportions for the primary effectiveness endpoint of 0.2 for the OCS treatment and 0.25 for the Control treatment, and power of 80%. Based on these specifications, the required sample size was determined to be 144 transplanted recipients per treatment group, or 288 total transplanted subjects. To ensure an

adequate number of subjects in the Per Protocol Population, the sample size was increased to a total of 300 transplanted subjects. Subjects will be enrolled until there are either 290 subjects in the Per Protocol Population or a total of 300 transplanted subjects, whichever comes first.

3.5. Changes to the Protocol-Specified Analyses

The sample size re-estimation proposed in the protocol will not be performed per FDA recommendation. Enrollment will be concluded at the original planned sample size of 300 patients as FDA has recommended ([redacted]).

As recommended by FDA, additional post-hoc exploratory analyses for the primary endpoint have been added to test for site poolability, with small sites pooled by US geographic region. ([redacted]).

Post-hoc tipping point sensitivity analyses have been added based on FDA's recommendation for the primary efficacy endpoint and the two secondary efficacy endpoints ([redacted]).

Two exploratory study populations have been added to the analyses. The exploratory mITT2 population will include an additional 43 subjects who have been transplanted off-study with a randomized organ, and the exploratory ITT population will include all subjects who have signed informed consent, been enrolled in the study, randomized, and the assigned liver preservation method has been initiated. An Exploratory analysis will be included for the mITT2 and ITT populations of patient and graft survival at 30 days post-transplant. ([redacted]).

Analyses of the primary effectiveness endpoints and secondary effectiveness endpoints by donor inclusion criteria will be performed.

The incidence of non-ischemic biliary complications in 30 days and in 6 months, defined using MedDRA terminology, will be reported ([redacted]).

Subgroup reporting has been added for Donor after Brain Death (DBD) transplants. The two subgroups used in recipient reporting are DBD transplants with total cross clamp time ≥ 6 hours and DBD transplants with total cross clamp time < 6 hours ([redacted]).

4. EFFECTIVENESS AND SAFETY ENDPOINTS

4.1. Primary Effectiveness Endpoint

Incidence of Early liver Allograft Dysfunction (EAD) or primary non-function, defined as presence of one or more of the following criteria:

- AST level > 2000 IU/ml within the first 7 postoperative days
- Bilirubin ≥ 10 mg/dl on postoperative Day 7
- INR ≥ 1.6 on postoperative Day 7
- Primary non-functioning graft within the first 7 days (defined as irreversible graft dysfunction requiring emergency liver re-transplantation or resulting in death, in the absence of immunologic or surgical causes)

4.2. Secondary Effectiveness and OCS Donor Liver Assessment Endpoints

- OCS donor liver assessment during perfusion, defined as, among donor livers preserved using OCS for the entire preservation period, the proportion of livers on which measurements of all of the following during perfusion were available on OCS device before transplant
  - Lactate level (every two hours + 20 mins. of time window)
  - Average bile production rate (based on total bile production volume and duration of OCS perfusion)
  - Hepatic Artery Pressure (continuously averaged every 30 minutes)
  - Portal Vein Pressure (continuously averaged every 30 minutes)
- Patient survival at Day 30 post-transplantation
- Patient survival at initial hospital discharge post liver transplantation

4.3. Other Endpoints

- Length of initial post-transplant ICU stay
- Length of initial post-transplant hospital stay
- Evidence of ischemic biliary complications diagnosed at 6 and at 12 months post-transplant
- Extent of reperfusion syndrome as assessed based on the rate of decrease of lactate over the following time points:
  - During a hepatic phase immediately before reperfusion of the transplanted liver
  - 30-40 minutes after hepatic artery and portal vein reperfusion of the transplanted liver
  - 90-120 minutes after reperfusion of the transplanted liver
- Pathology sample score for liver tissue samples taken at the following time points (applies to both OCS and Control arms):
  - Donor liver pre-retrieval
  - Post-OCS and Control preservation at the end of back preparation and immediately before the start of re-implantation

– 90-120 minutes after reperfusion of the transplanted liver

4.4. Safety Endpoint

Safety will be analyzed principally by examination of the frequency of liver graft-related serious adverse events (SAEs) up to the 30-day follow-up after transplantation. This endpoint is defined as the number of liver-graft related serious adverse events through 30 days post-liver transplantation per subject, consisting of the following serious adverse events (at most one per type per person):

- Primary non-function (defined as irreversible graft dysfunction requiring emergency liver re-transplantation or death with the first 10 days, in the absence of immunologic or surgical causes)
- Ischemic biliary complications (ischemic biliary strictures and non-anastomotic bile duct leaks)
- Vascular complications (liver-graft related coagulopathy, hepatic artery stenosis, hepatic artery thrombosis, and portal vein thrombosis)
- Liver allograft infections (liver abscess, cholangitis, etc.)

5. STATISTICAL CONSIDERATIONS

5.1. General Methodology

All statistical analyses will be performed and all tables and listings will be produced using SAS® Version 9.3 or higher.

Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized using frequencies and percentages. For continuous data the minimum and maximum will use the same decimal accuracy as the raw data. The mean and median will use 1 more decimal place than the raw data, and the standard deviation will use 2 more decimal place than the raw data. For categorical data, percentages will be reported to 1 decimal place. P-values will be reported to 4 decimal places. P-values less than 0.0001 will be displayed as <0.0001 in the tables.

All statistical tests will be performed at the 0.05 significance level unless otherwise noted.

All data collected will be included in the data listings. Data listings will be sorted by treatment arm and either by recipient ID or by donor ID, as appropriate.

5.2. Adjustments for Covariates

No adjustments for covariates will be made in the statistical analyses for the primary and secondary endpoints.

An exploratory logistic regression analysis that adjusts for potential baseline differences in MELD score, whether or not the donor was a DCD donor, and donor age (years), all of which are known to impact outcomes for liver transplant recipients, will be performed. The classification of pooled sites in the analysis of the primary effectiveness endpoint with pooled investigational site data is contained in Appendix 1 of this document.

5.3. Handling of Dropouts and Missing Data

If there are any missing data, multiple imputation (MI) methods will be used for patients with missing outcomes for the primary effectiveness endpoint and for the secondary effectiveness endpoints of patient survival at Day 30 post-transplantation and patient survival at initial hospital discharge post liver transplantation. Using SAS® PROC MI, the logistic regression method of imputation will be used with treatment group and the covariates listed below as explanatory variables. This method of multiple imputation is appropriate for a binary dependent variable with explanatory variables following a monotone missing pattern and assumes that the data for the dependent variable are missing at random (MAR). For imputations based on the Per Protocol and the Modified Intent-to-Treat populations twenty imputation data sets will be generated. For each imputed dataset, PROC FREQ of SAS® will be used to obtain the success proportion and the corresponding standard error for each treatment. PROC MIANALYZE of SAS® will be used to combine the results from the imputed datasets to produce an overall estimate of the true success proportion and the corresponding 95% confidence interval for each treatment. The p-values for the tests for non-inferiority and superiority from normal approximation tests will also be presented. If the imputed endpoint values from all imputed datasets are identical, the frequency values obtained prior to the PROC MIANALYZE step will be used in the analysis.

The following covariates will be used to impute missing data outcomes:

- Donor after cardiac death (DCD donor): (Yes, No)
- Donor age: (< 40 years, ≥ 40 years)
- Steatotic liver: (≤ 20% macrosteatosis at time of retrieval, > 20% macrosteatosis at the time of retrieval).
- Recipient gender: (Male, Female)
- Recipient age

5.4. Tipping Point Sensitivity Analysis

For the primary efficacy endpoint and each of the two secondary efficacy endpoints, assuming the Per Protocol Population analysis with imputation of missing data results in rejection of the null hypothesis in favor of non-inferiority, a tipping point sensitivity analysis based on the Per Protocol Population will be used to assess the effect of missing data. In the tipping point analysis, the penalty will be set for OCS subjects only. First, the MI analysis described in Section 5.3 will be run. Then, for the OCS subjects with missing data who were categorized as a success (not having EAD) after the MI analysis, one such subject will be categorized as a failure (having EAD), and the test for non-inferiority will be performed. Then it will be assumed that two OCS subjects with missing data had EAD, and the test for non-inferiority will be performed, etc. The "tipping point" is the number of OCS subjects categorized as having had EAD where a statistically significant result in favor of non-inferiority first no longer occurs. If the imputed endpoint values from all imputed datasets are identical, the frequency values obtained prior to the PROC MIANALYZE step will be used in the analysis.

5.5. Pooling by Investigational Site

An additional analysis of the primary endpoint will evaluate pooling by recipient investigational site. This analysis will be performed on observed data using PROC LOGISTIC of SAS® on the mITT and Per-Protocol populations. The model will include treatment arm (OCS or Control), pooled site, MELD score, DCD donor (Yes or No), donor age (years), and the interaction of treatment arm and pooled site. The Wald Chi-square p-values (from the Type 3 Analysis of Effects) will be presented for pooled site and the treatment by pooled site interaction term in the model. The significance level for the test of the interaction of treatment by pooled site will be α=0.15. The p-values for MELD score, donor age, and DCD donor will not be reported.

A pooled site variable will be created in order to pool small sites geographically. The five investigational sites with the highest number of transplanted subjects will not be pooled. The remaining sites will be pooled by U.S. geographic region (Northeast, South, and West). The pooled sites by geographic region will have a minimum of 20 transplanted subjects (Ref. Appendix 1.).

5.6. Interim Analyses

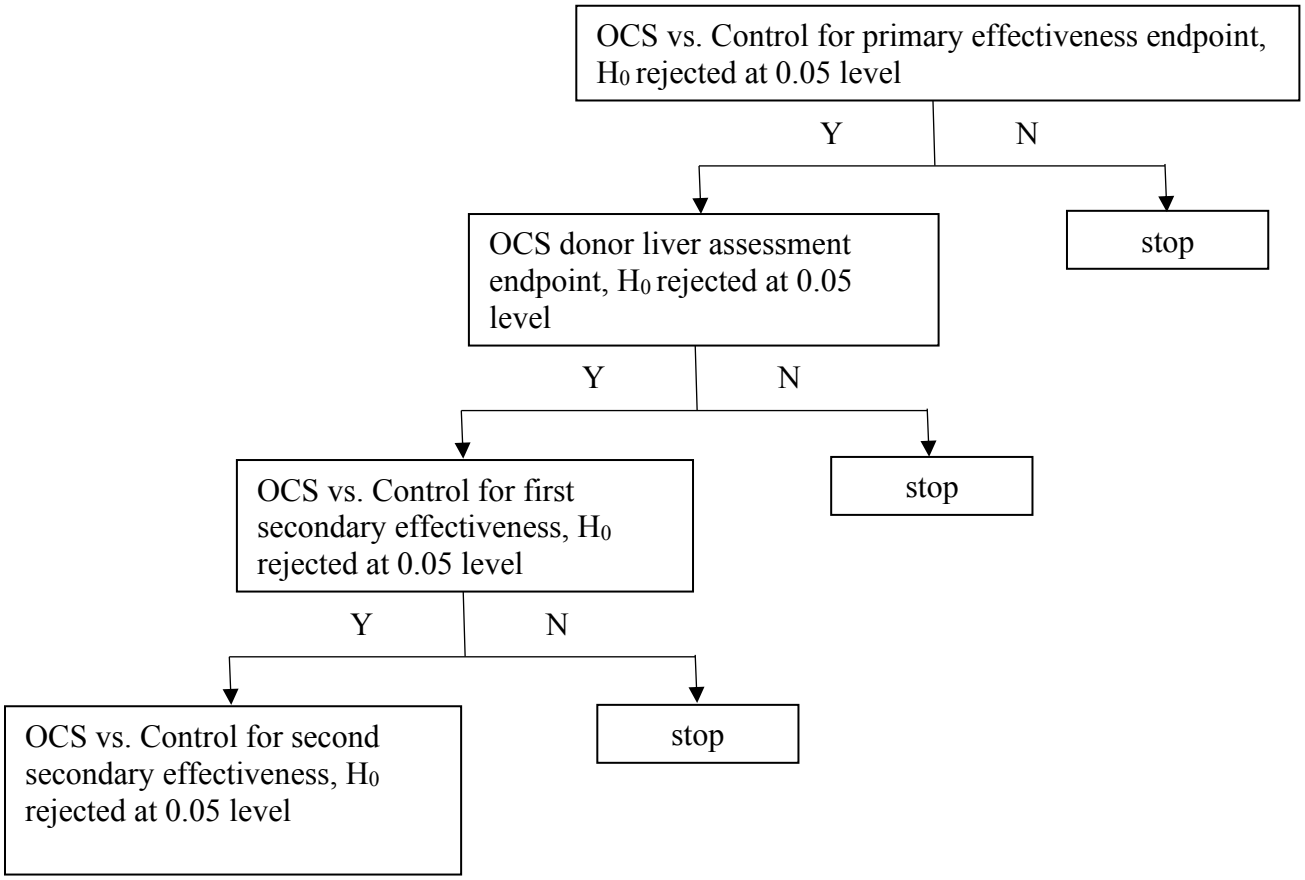
For regulatory purposes, descriptive summaries and/or data listings of key data will be provided to the FDA based on the first 10 transplanted liver recipients in Part A of the study after they have completed 30 days post-transplantation and on the first 20 transplanted liver recipients in Part A of the study after they have completed 30 days post-transplantation.

5.7. Multicenter Study

Subjects will be recruited from up to twenty-five (25) investigative sites worldwide.

5.8. Multiple Comparisons / Multiplicity

No adjustments for multiple comparisons/multiplicity will be made. Because fixed sequence testing will be used for the secondary effectiveness endpoints, no adjustment for the multiplicity of these endpoints needs to be made. The fixed sequence testing is shown below.



5.9. Examination of Subgroups

Subgroup analyses of the primary effectiveness endpoint and the secondary effectiveness endpoints will be performed for the following subgroups of patients:

- DCD (donation after circulatory death) patients (Yes/No)
- Fatty liver patients (Macrosteatosis: <= 20%, >20%)

- Donor Age (<=50 years old, > 50 years old)
- Recipient MELD score (<=25, >25)
- Donor organ total cross-clamp time < 6 hours, >= 6 hours (DBD donors only)
- Donor Inclusion Criteria (each criterion separately, one criteria, multiple criteria)

No data imputation or statistical tests will be performed for the subgroup analyses for the effectiveness endpoints.

Additional subgroup analyses will be performed for selected demographic and baseline comparisons (recipient and donor) and for adverse events (recipient). The recipient subgroup analyses will use the subgroups defined above excluding donor inclusion criteria, while donor subgroup analyses will exclude both the MELD score and donor inclusion criteria subgroups. For these additional subgroup analyses, statistical testing will only be performed for recipient and donor demographic and baseline characteristics to compare treatment groups.

6. ANALYSIS POPULATIONS

6.1. Per Protocol Population

The Per Protocol (PP) Population will consist of all randomized subjects who are transplanted and have no major protocol violations and for whom the donor liver received the complete preservation procedure as per the randomization assignment. The major protocol violations that will exclude a subject from this population are the following:

- Ineligible for the study according to the recipient inclusion and exclusion criteria
- Ineligible for the study according to the donor organ inclusion and exclusion criteria
- Subject is transplanted with a liver with preservation other than that to which the subject was randomized
- Failure to complete adequate post-transplant assessments to support the primary, secondary or safety endpoints
- Other major protocol violations

The final designation of major protocol violations resulting in an exclusion from the PP Population will be made during a blinded review by the CEC prior to database lock.

In analyses based on the PP Population, subjects will be analyzed as randomized. The primary analysis of the primary and secondary effectiveness endpoints and of other endpoints will be based on the PP Population.

6.2. Modified Intent-to-Treat Population

The Modified Intent-to-Treat Population (mITT) will consist of all randomized subjects who are transplanted in the PROTECT study. In analyses based on mITT Population, subjects will be analyzed as randomized. The mITT Population analyses will be considered secondary analyses of effectiveness.

6.3. As Treated Population

The As Treated Population (AT) will consist of all treated subjects, i.e., all subjects who are transplanted in the study with a donor liver preserved with either OCS or Control. In analyses based on this population, subjects will be analyzed as treated. A subject who receives a liver with some preservation with OCS and some with standard of care will be classified as OCS, because any donor liver preserved with OCS at any time during the preservation process will be classified as OCS. Analyses of safety endpoints will be performed based on the AT Population

6.4. Donor Liver Population

The Donor Liver Population will consist of all donor livers for which the potential recipient was randomized and which have preservation initiated using OCS or Control in the PROTECT study. A liver with some preservation with OCS and some with standard of care will be analyzed as preserved with OCS.

6.5. Modified Intent-to-Treat 2 Population

The Modified Intent-to-Treat 2 Population (mITT2) will consist of all randomized subjects who are transplanted in either the PROTECT study or outside of the PROTECT study. In analyses based on the mITT2 Population, subjects will be analyzed as randomized. The mITT2 Population analyses will be considered exploratory analyses.

6.6. Intent-to-Treat Population

The Intent-to-Treat Population (ITT) will consist of subjects who have signed informed consent, been enrolled in the study, randomized, and the assigned liver preservation method has been initiated. In analyses based on the ITT Population, subjects will be analyzed as randomized. The ITT Population analyses will be considered exploratory analyses.

7. SUBJECT AND DONOR LIVER DISPOSITION

The recipient subject accountability table will report the numbers of screened subjects, subjects not transplanted in the PROTECT study (and reason), and subjects in each analysis population. The table will also present the numbers and percentages of subjects who completed the study and who discontinued from the study early (before Month 24), along with the primary reason for discontinuation. At each scheduled follow-up evaluation (Day 7, Day 30, Month 6, Month 12, and Month 24) the expected number of subjects (defined as subjects whose cutoff date – transplant date is greater than the end of the interval and excluding discontinuations as of the last follow-up visit), the number completing the study through the follow-up timepoint, and the number discontinuing the study after the prior follow-up evaluation will be reported.

The number and percentage of subjects rerandomized will be presented. The number of rerandomizations per subject will be summarized using counts and percentages.

The donor liver disposition table will summarize the total number of donor livers, donor reallocation, the number of screened donor livers, the number of livers transplanted off study, the number of livers randomized but not transplanted and the reason, and the number of livers transplanted in the PROTECT study with and without randomization. The number of livers in the Donor Liver and mITT populations will be reported. The number of organs preserved for the entire preservation period per the randomization assignment and the status of organs not preserved per the randomization assignment will also be presented.

8. PROTOCOL DEVIATIONS

Protocol deviations will be summarized by type of deviation and overall using counts and percentages. Two categories will be used to report protocol deviations: major protocol violations resulting in exclusion from the Per Protocol Population and minor protocol deviations. The total number of subjects with one or more major protocol violations and the total number of subjects with one or more minor protocol deviations will also be reported. Results will be presented by treatment group and overall.

9. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

9.1. Recipient Demographic and Baseline Characteristics

Recipient demographic and baseline characteristics will be summarized for the AT and PP populations. Frequencies and percentages will be presented for categorical variables. Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables. Treatment groups will be compared statistically (chi-square test for categorical variables and two-sided, two-sample t-tests for continuous variables). Recipient demographic and baseline characteristics will also be reported for the subgroups indicated in Section 5.9 and compared statistically as noted above.

Recipient factors (history of hepatitis C and history of liver cancer), history of diabetes, type of diabetes (if present), and primary etiology of liver failure at screening will be summarized for the AT and PP populations using frequencies and percentages. This information will also be summarized for the subgroups indicated in Section 5.9.

9.2. Donor Demographic and Baseline Characteristics

Donor demographic and baseline characteristics will be summarized for the Donor Liver Population (as treated and PP). Frequencies and percentages will be presented for categorical variables. Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables. Treatment groups will be compared statistically (chi-square test for categorical variables and two-sided, two-sample t-tests for continuous variables). Donor demographic and baseline characteristics will also be summarized for the subgroups indicated in Section 5.9 (with the exception of MELD score) and compared statistically as noted above.

Donor medical history, reported as a history of specific medical conditions, will be summarized for the Donor Liver Population (as treated and PP) using frequencies and percentages. This information will also be summarized for the subgroups noted above.

Donor cause of death, presence of abdominal trauma at death, whether the donor is a DCD, and whether the donor experienced cardiac arrest will be summarized for the Donor Liver Population (as treated) using frequencies and percentages. This information will also be summarized for the subgroups noted above.

Liver enzymes (bilirubin, AST, ALT, GGT, alkaline phosphatase, INR, and final donor arterial lactate level) from the assessment before retrieval in the donor's abdomen, the biopsy from the assessment before instrumentation on the OCS, and liver perfusion parameters will be summarized for the Donor Liver Population (as treated) using descriptive statistics for continuous variables and frequencies and percentages for categorical variables.

10. DONOR OPERATIVE CHARACTERISTICS, OCS INSTRUMENTATION, AND OCS PERFUSION

Donor operative characteristics and OCS instrumentation will be summarized using descriptive statistics for continuous variables and frequencies and percentages for categorical variables. Total cross clamp time, total ischemic time and presence of surgical complications/tears during retrieval will be summarized by treatment group. For total cross clamp time, treatment groups will be compared statistically using a two-sided, two-sample t-test.

Pre-OCS ischemic time, post-OCS ischemic time, and OCS perfusion time (in minutes) will be summarized for the OCS treatment group using descriptive statistics.

Liver enzymes (total bilirubin, AST, ALT, GGT, alkaline phosphatase, INR, and arterial lactate level) will be summarized at OCS baseline and at the OCS final. Bile volume will be summarized at the OCS final only. Both will be summarized using descriptive statistics.

The number and percentage of donor livers in the Donor Liver Population for which there was a device malfunction will also be presented.

The analyses above will be performed for the Donor Liver Population (as treated) with the exception of the device malfunction analysis, which will be performed for the Donor Liver Population (as randomized).

11. TRANSPLANT CHARACTERISTICS AND RECIPIENT POST-TRANSPLANT HOSPITAL/ICU STAY

Transplant characteristics will be summarized using frequencies and percentages for categorical variables and descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for continuous variables.

The initial post- transplant Hospital/ICU stay duration and the re-admission Hospital/ICU stay duration will be summarized using descriptive statistics.

The initial post-transplant hospital stay is defined as the duration in days from ICU admission to post transplant hospitalization discharge.

The initial post-transplant ICU stay is defined as the duration in hours from ICU admission to initial ICU clinical order discharge. If the initial ICU clinical order discharge date and time are missing, the actual ICU discharge date and time will be substituted. If the time is missing, a value of 23:59 will be used.

These analyses will be performed for the PP, mITT and AT populations.

12. ANALYSIS OF EFFECTIVENESS ENDPOINTS

12.1. Primary Effectiveness Endpoint

The primary effectiveness endpoint for this study is Early Liver Allograft Dysfunction (EAD), defined as presentation of one or more of the following criteria:

- AST level > 2000 IU/ml within the first 7 postoperative days
- Bilirubin ≥ 10 mg/dl on postoperative Day 7
- INR ≥ 1.6 on postoperative Day 7
- Primary non-functioning graft within the first 7 days (defined as irreversible graft dysfunction requiring emergency liver re-transplantation or resulting in death, in the absence of immunologic or surgical causes)

The primary hypothesis for this study is that the OCS treatment is non-inferior to the standard of care treatment with respect to this endpoint. The primary statistical hypotheses are as follows:

H_{10}: $\pi_{1,OCS} \geq \pi_{1,CONTROL} + \delta$ and
H_{11}: $\pi_{1,OCS} < \pi_{1,CONTROL} + \delta$,

where $\pi_{1,OCS}$ and $\pi_{1,CONTROL}$ are the true proportions of subjects with Early Liver Allograft Dysfunction for the OCS and standard of care treatments, respectively, and δ is the non-inferiority margin, which is here taken to be 0.075.

The primary effectiveness endpoint will be analyzed by calculating, for each treatment group, the sample proportion of subjects meeting the primary effectiveness endpoint, as well as an exact (Clopper-Pearson) 95% confidence interval for the corresponding population percentage. The 95% exact unconditional one-sided upper confidence bound based on the Farrington and Manning score statistic will be calculated for the difference between the two population proportions ($\pi_{1,OCS} - \pi_{1,CONTROL}$). An upper confidence bound less than $\delta = 0.075$ will result in rejection of the null hypothesis (H_{10}) in favor of the alternative hypothesis (H_{11}) and the demonstration of non-inferiority of OCS to control for the primary effectiveness endpoint. In the event non-inferiority is demonstrated, Fisher's exact test (two-sided) will be used to test for superiority.

This endpoint will be analyzed using the Per Protocol and mITT Populations. The Per Protocol analysis will be considered the primary analysis. Analyses will first be performed without any imputation of missing data. If there are any missing data for this endpoint, multiple imputation methods will be used for data imputation for any patients with missing values for this endpoint. The multiple imputation methods are described in Section 5.3.

Assuming the Per Protocol Population analysis of the primary efficacy endpoint with imputation of missing data results in rejection of the null hypothesis in favor of non-inferiority, a tipping point sensitivity analysis based on the Per Protocol Population as described in Section 5.4 will be used to assess the effect of missing data. A tipping point analysis will also be performed using the mITT population if the analysis of the primary efficacy endpoint with imputation of missing data based on the mITT Population results in rejection of the null hypothesis in favor of non-inferiority.

In order to examine poolability by investigational site, an analysis of the primary effectiveness endpoint including terms for treatment, MELD score, DCD donor (Yes or No), donor age (years), pooled site, and the interaction of pooled site and treatment will be performed as described in Section 5.5. This analysis will be performed for both the Per Protocol and mITT populations.

Subgroup analyses of the primary effectiveness endpoint will be performed for the subgroups indicated in Section 5.9. No data imputation or statistical tests will be performed for these subgroup analyses. In addition, analyses of the primary effectiveness endpoint by donor inclusion criteria will be performed using observed data. In these analyses, the endpoint will be reported for the proportion of subjects meeting each individual donor inclusion criteria, a single donor exclusion criteria, multiple donor exclusion criteria, and at least one donor exclusion criteria. No data imputation or statistical tests will be performed for these analyses based on donor inclusion criteria. The subgroup analyses and the donor inclusion analyses will be performed for both the Per Protocol and mITT populations.

12.2. Secondary Effectiveness and OCS Donor Liver Assessment Endpoints

The secondary effectiveness and OCS donor liver assessment endpoints for this trial are as follows:

- OCS donor liver assessment during perfusion, defined as, among donor livers preserved using OCS for the entire preservation period, the proportion of livers on which measurements of all of the following during perfusion will be available on OCS device before transplant
    - Lactate level (every two hours +20 mins. of time window)
    - Average bile production rate (based on total bile production volume and duration of OCS perfusion)
    - Hepatic Artery Pressure (continuously averaged every 30 minutes)
    - Portal Vein Pressure (continuously averaged every 30 minutes)
- Patient survival at Day 30 post-transplantation
- Patient survival at time of initial hospital discharge post-transplantation

The null and alternative hypotheses for the OCS donor liver assessment during perfusion endpoint are:

H_0: $\pi_3 \leq 0.85$ and
H_1: $\pi_3 > 0.85$,

respectively, where π_3 is the true proportion of livers, among donor livers preserved using OCS for the entire preservation period, on which measurements of lactate level, average bile production rate, Hepatic Artery Pressure and Portal Vein Pressure during perfusion were available on OCS device before transplant.

This secondary endpoint of OCS donor liver assessment during organ perfusion will be analyzed by calculating the sample proportion of donor livers placed on OCS meeting the criteria for this endpoint, as well as an exact (Clopper-Pearson) 95% one-sided lower confidence bound for the corresponding population proportion. A lower confidence bound greater than 0.85 will result in rejection of the null hypothesis in favor of the alternative hypothesis and demonstration that the true proportion is greater than 0.85 for the OCS donor liver assessment endpoint. If information for any of the four measurements is missing, the donor liver will be classified as not meeting the OCS donor liver assessment criteria. This secondary endpoint will be analyzed using the Donor Liver Population but limited to livers preserved with OCS for the entire preservation period.

Each secondary effectiveness endpoint will be summarized by treatment group using the count and percentage and the exact (Clopper-Pearson) 95% confidence interval for the true percentage based on the binomial distribution. The secondary effectiveness endpoints will be analyzed using the Per Protocol and mITT Populations, with the Per Protocol analysis being considered the primary analysis.

The statistical hypotheses for the first secondary effectiveness endpoint, patient survival at Day 30 post-transplantation, are as follows:

H_{20}: $\pi_{2,OCS} \leq \pi_{2,CONTROL} - \delta$ and
H_{21}: $\pi_{2,OCS} > \pi_{2,CONTROL} - \delta$,

where $\pi_{2,OCS}$ and $\pi_{2,CONTROL}$ are the true proportions of subjects surviving to Day 30 post-transplantation for the OCS and standard of care treatments, respectively, and δ is the non-inferiority margin, which is here taken to be 0.075. This endpoint will be analyzed by calculating the 95% one-sided upper confidence bound based on the Farrington and Manning score statistic for the difference between the two population proportions ($\pi_{2,CONTROL} - \pi_{2,OCS}$). An upper confidence bound less than $\delta = 0.075$ will result in rejection of the null hypothesis (H_{20}) in favor of the alternative hypothesis (H_{21}) and demonstration of non-inferiority of OCS to Control. In the event non-inferiority is demonstrated, Fisher's exact test (two-sided) will be used to test for superiority.

The second secondary effectiveness endpoint, patient survival at initial hospital discharge post liver transplantation, will be analyzed in a manner analogous to the first secondary effectiveness endpoint with the same non-inferiority margin of 0.075.

Because fixed sequence testing will be used for the secondary endpoints, no adjustment for the multiplicity of these endpoints needs to be made. The endpoints will be tested in the order listed above. The test for non-inferiority for the first secondary effectiveness endpoint will be performed only if the null hypothesis has been rejected for the OCS donor liver assessment endpoint. The test for non-inferiority for the second secondary effectiveness endpoint will be performed only if the null hypothesis has been rejected in favor of the alternative hypothesis of non-inferiority of the OCS treatment to the Control treatment for the first secondary effectiveness endpoint. Similarly, the test for superiority for the second secondary effectiveness endpoint will be performed only if the null hypothesis of equality has been rejected in favor of superiority of the OCS treatment to the Control treatment for the first secondary effectiveness

endpoint (and non-inferiority has been demonstrated for the given secondary effectiveness endpoint). Due to statistical power limitations, it is not expected that non-inferiority will be demonstrated for patient survival at day 30 or at initial hospital discharge.

Multiple imputation methods, as described in Section 5.3, will be used for data imputation for patients with missing values for the patient survival secondary endpoints.

Assuming the Per Protocol Population analysis of a patient survival secondary endpoint with imputation of missing data results in rejection of the null hypothesis in favor of non-inferiority, a tipping point sensitivity analysis based on the Per Protocol Population as described in Section 5.4 will be used to assess the effect of missing data for the relevant patient survival secondary endpoint. A tipping point sensitivity analysis will also be performed using the mITT population if the analysis of a patient survival secondary efficacy endpoint with imputation of missing data based on the mITT Population results in rejection of the null hypothesis in favor of non-inferiority.

Subgroup analyses of the secondary effectiveness endpoints will be performed for the subgroups indicated in Section 5.9. No data imputation or statistical tests will be performed for these subgroup analyses. In addition, analyses of each secondary effectiveness endpoint by donor inclusion criteria will be performed using observed data. In these analyses, the endpoint will be reported for the proportion of subjects meeting each individual donor inclusion criteria, a single donor exclusion criteria, multiple donor exclusion criteria, and at least one donor exclusion criteria. No data imputation or statistical tests will be performed for these analyses based on donor inclusion criteria. The subgroup analyses and the donor inclusion analyses will be performed for both the Per Protocol and mITT populations.

13. ANALYSIS OF SAFETY

Safety analyses for adverse events will be based on CEC-adjudicated adverse events.

Safety will be analyzed principally by examination of the frequency of liver graft-related serious adverse events (SAEs) up to the 30-day follow-up after transplantation. This endpoint is defined as the number of liver-graft related serious adverse events through 30 days post-liver transplantation per subject, consisting of the following serious adverse events (at most one per type per person):

- Primary non-function (defined as irreversible graft dysfunction requiring emergency liver re-transplantation or death within the first 10 days, in the absence of immunologic or surgical causes)
- Ischemic biliary complications (ischemic biliary strictures and non-anastomotic bile duct leaks)
- Vascular complications (liver graft-related coagulopathy, hepatic artery stenosis, hepatic artery thrombosis, and portal vein thrombosis)
- Liver allograft infections (liver abscess, cholangitis, etc.)

This endpoint will be summarized by treatment group using descriptive statistics. For each treatment group, a 95% confidence interval for the mean based on the t-distribution will be presented. Also, a 95% confidence interval based on the t-distribution will be presented for the difference in means between the two treatments.

For the number of liver graft-related SAEs, the statistical hypotheses are as follows:

H_{30}: $\mu_{OCS} \geq \mu_{CONTROL} + \delta$ and
H_{31}: $\mu_{OCS} < \mu_{CONTROL} + \delta$,

where μ_{OCS} and $\mu_{CONTROL}$ are the true mean numbers of liver graft-related SAEs up to the 30-day follow-up after transplantation per subject with the OCS and standard of care treatments, respectively, and δ is the non-inferiority margin, which is here taken to be 1.0. The safety endpoint will be analyzed using a one-sided, two-sample t-test with an alpha level of 0.05. If non-inferiority is demonstrated, a corresponding (two-sided) two-sample t-test of superiority will be performed.

This endpoint will be analyzed based on the As Treated Population.

For each of the four categories of liver graft-related SAEs listed above, the number of subjects with an event and the number of events up to the 30-day follow-up after transplantation will be summarized.

In addition, the numbers and percentages of subjects experiencing at least one treatment-emergent adverse event (TEAE) in the following categories will be tabulated by treatment group: liver graft-related TEAEs, treatment-related (definitely or probably-related) TEAEs, serious TEAEs, and serious liver graft-related TEAEs. The number of treatment-emergent liver graft-related adverse events, treatment-emergent serious adverse events (within 30 days post-

transplant and overall), treatment-emergent serious liver graft-related adverse events (within 30 days post-transplant and overall), treatment-emergent adverse events resulting in study discontinuation, and treatment-emergent serious adverse events with an outcome of death (within 30 days post-transplant and overall) will be tabulated by system organ class and preferred term using MedDRA (Version 13.0 or higher). Liver graft-related TEAEs and liver graft-related serious TEAEs will also be tabulated at the event level by system organ class and preferred term and the relationship of the liver graft-related adverse event to the investigational treatment using counts and percentages. Similar analyses at the event level will be performed by the severity of the adverse event.

The adverse event analyses above will also be presented by subgroup.

An exploratory analysis of the frequency of non-ischemic biliary complications through 30 days post-liver transplantation per subject will be performed. This endpoint will be summarized by treatment group using descriptive statistics. For each treatment group, a 95% confidence interval for the mean based on the t-distribution will be presented. Also, a 95% confidence interval based on the t-distribution will be presented for the difference in means between the two treatments.

14. OTHER ENDPOINTS AND ADDITIONAL REPORTING

Other endpoints to evaluated for the PP, mITT, and AT populations are described below:

- **Evidence of ischemic biliary complications diagnosed within 6 months and within 12 months post-transplant:**
  Ischemic biliary complications diagnosed within 6 and 12 months post-transplant will be summarized by prevalence (subject-based) and event-rates (per patient-year). The ratio of event rates between treatment groups (OCS/Control) will also be reported. Treatments will be compared statistically using a chi-square test for prevalence of events (subject-based) and Poisson regression (PROC GENMOD) for event-rates. Statistical significance will be demonstrated if the p-value is less than 0.05. A 95% confidence interval will be presented for the ratio of event rates (OCS/Control).

- **Evidence of non-ischemic biliary complications diagnosed within 30 days and within 6 months post-transplant:**
  Exploratory analyses for the incidence of non-ischemic biliary complications within 30 days and within 6 months post-transplant will be analyzed in a manner similar to the above analysis for ischemic biliary complications. Non-ischemic biliary complications will be defined based on MedDRA Lowest Level Term (LLT) category.

- **Extent of reperfusion syndrome as assessed based on the rate of decrease of lactate over the following time points:**
  - During a hepatic phase immediately before reperfusion of the transplanted liver
  - 30-40 minutes after hepatic artery and portal vein reperfusion of the transplanted liver
  - 90-120 minutes after reperfusion of the transplanted liver

  The reperfusion rate will be estimated for transplanted recipients with a measurement prior to reperfusion of the transplanted liver and at least one of the two additional timepoints. The per-subject slope will be estimated using linear regression modeling across the timepoints. Reperfusion syndrome is defined as a slope > 0. Subjects with a slope less than or equal to 0 will be classified as not having reperfusion syndrome.

  Reperfusion syndrome will be summarized by prevalence (subject-based). Treatments will be compared statistically using a chi-square test for prevalence of events, with statistical significance demonstrated if the p-value is less than 0.05. A 95% confidence interval will be presented for the difference in prevalence (OCS – Control).

- **Average pathology sample score (single score per liver) for liver tissue samples as defined in the protocol taken at the following time points (applies to both OCS and Control arms):**
  - Donor liver pre-retrieval
  - Post-OCS and Control preservation at the end of back preparation and immediately before the start of re-implantation

- 90-120 minutes after reperfusion of the transplanted liver

Average pathology sample score will be summarized by treatment group using descriptive statistics. The difference in means between treatment groups will also be reported. 95% confidence intervals based on the t-distribution will be presented for the true means for each treatment and for the true difference in means between treatments (OCS – Control). Treatments will be compared statistically using a two-sided, two-sample t-test. Statistical significance will be demonstrated if the p-value is less than 0.05.

Additional evaluations for the PP, mITT, AT, mITT2, and ITT populations are described below:

- **Follow-up status**

  For the PP, mITT, and AT Populations subject and liver graft status will be reported at the 30 day, 6 month, 12 month, and 24 month visits. Subject survival and liver graft survival will be tabulated by treatment group at each follow-up visit using counts and percentages. The number of subjects with liver graft related re-hospitalization between the 30 day and 6 month follow-up visits and between the 6 month and 12 month follow-up visits will be summarized using counts and percentages.

  Kaplan-Meier estimated probabilities of recipient survival and liver graft survival will be presented for the PP, mITT, and AT Populations at the following nominal timepoints: 30 days, 6 months, 12 months, and 24 months post-transplantation.

  Recipient and liver graft status will be reported at 30 days post-transplant for the mITT2 and ITT populations.

15. REFERENCES

None.

APPENDIX 1. LIST OF POOLED SITES

Site name	# of patients	Pooled site	# of patients (Pooled)
LV-01-[redacted]	69	[redacted]	69
LV-02-[redacted]	46	[redacted]	46
LV-04-[redacted]	43	[redacted]	43
LV-06-[redacted]	48	[redacted]	48
LV-09-[redacted]	19	[redacted]	19
LV-10-[redacted]	12	[redacted]	20
LV-11-[redacted]	7	[redacted]	
LV-17-[redacted]	1	[redacted]	
LV-18-[redacted]	0	[redacted]	
LV-03-[redacted]	5	[redacted]	28
LV-13-[redacted]	7	[redacted]	
LV-14-[redacted]	9	[redacted]	
LV-20-[redacted]	7	[redacted]	
LV-05-[redacted]	5	[redacted]	25
LV-07-[redacted]	5	[redacted]	
LV-08-[redacted]	6	[redacted]	
LV-12-[redacted]	4	[redacted]	
LV-15-[redacted]	4	[redacted]	
LV-16-[redacted]	0	[redacted]	
LV-19-[redacted]	1	[redacted]	