STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: CLN-PRO-V006

An Assessment of Humacyte's Human Acellular Vessel in Patients Needing Renal Replacement Therapy: A Comparison with ePTFE Grafts as Conduits for Hemodialysis (HUMANITY)

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SAP REVISIONS

The following table details the changes made to the SAP version 2.0 (13JAN2017) to provide clarifications on some of the analysis methods and to match protocol amendment v5.0.

Protocol Version # Date	SAP Section	Modification	Description and Rationale
5.0 08AUG2018	Abbreviation and Terms	Added "BMI" to the list	Updated for the analysis
5.0 08AUG2018	1.0	Changed the primary analysis from 12 months to 18 months post-implantation	Updated to match the protocol.
5.0 08AUG2018	2.2.2.4	Changed "rupture" to "spontaneous rupture".	Updated to match the protocol.
5.0 08AUG2018	2.2.2.5	Changed "rupture" to "spontaneous rupture". Added "Iatrogenic injuries are not an Event of Special Interest and should be reported as an AE". Added "Steal syndrome"	Updated to match the protocol.
5.0 08AUG2018	4.0	Removed languages for Chi-square tests and Cochran-Mantel-Haenszel test. Changed 12 months to 18 months for the primary analysis	This was done to be consistent with the planned analysis for the study and to match the protocol.
5.0 08AUG2018	4.2	Edited the definition for the Per Protocol analysis set	Updated to match the protocol.
5.0 08AUG2018	5.2	Added "major" to protocol deviations.	Updated for clarification.
5.0 08AUG2018	5.3	Added body mass index (BMI) calculation	This was done to be consistent with the planned analysis for the study

Protocol Version # Date	SAP Section	Modification	Description and Rationale
5.0 08AUG2018	5.6	Replaced "WHO drug name" with "default Anatomical, Therapeutic, and Chemical (ATC) class".	Updated for clarification.
5.0 08AUG2018	6.1	Changed 12 to 18 months after implantation for the primary efficacy endpoint Changed "If the lower limit of the two-sided 95% confidence interval for the hazard ratio is greater than the corresponding non-inferiority bound" to " If the upper limit of the two-sided 95% confidence interval for the hazard ratio is less than the corresponding non-inferiority bound"	This was done to match the protocol and for clarification

Protocol Version # Date	SAP Section	Modification	Description and Rationale
5.0 08AUG2018	6.2	Changed "Interventions required to achieve/maintain Secondary Patency." to" Interventions required that successfully achieved/maintained Secondary Patency." Added language for checking overdispersion and using negative binomial regression if overdispersion is present Added analysis for failed interventions. Removed "Dichotomous data will be analyzed using Pearson's chi-square test to compare treatment groups." Changed "1 year" to "18 months"	This was done for clarification, and to be consistent with the planned analysis for the study.
5.0 08AUG2018	6.4	Added more details for sub-group analysis.	This was done for clarification, and to be consistent with the planned analysis for the study.
5.0 08AUG2018	7.1	Added an additional definition for exposure during the study period, and modified the original exposure definition.	This was done for clarification, and to be consistent with the planned analysis for the study.
5.0 08AUG2018	7.2	Added details for TEAE derivation.	This was done for clarification.
5.0 08AUG2018	7.2.5	Added language for checking overdispersion and using negative binomial regression if overdispersion is present	This was done for clarification, and to be consistent with the planned analysis for the study.

Protocol Version # Date	SAP Section	Modification	Description and Rationale
5.0 08AUG2018	7.2.6	Removed original analysis described in this section. Added new analysis for true aneurysms, pseudo-aneurysms, all aneurysms, and steal syndrome.	This was done to be consistent with the planned analysis for the study.
5.0 08AUG2018	7.5	Changed "each visit" to "Screening"	This was done for clarification.
5.0 08AUG2018	8	Added time to first cannulation and modified the language	This was done to be consistent with the planned analysis for the study.
5.0 08AUG2018	9	Added this section for CEC analysis	This was done to be consistent with the planned analysis for the study.
5.0 08AUG2018	11	Updated this section to provide rationale for changing the 12 month to 18 months post-implantation for the primary and secondary analyses.	Updated to match the protocol

The table below details the changes made to the SAP version 3.0 (27AUG2018) to be consistent with planned analysis.

Protocol Version # Date	SAP Section	Modification	Description and Rationale
5.0 08AUG2018	6.3	Added Section 6.3 for sensitivity analysis	Updated to reflect planned analysis for the study.
5.0 08AUG2018	6.4, 6.5, 6.6	Changed the original section numbers of 6.3, 6.4, and 6.5 to new section numbers of 6.4, 6.5, and 6.6, respectively.	After adding the new Section 6.3 for sensitivity analysis, the original section numbers were moved up accordingly.

The table below details the changes made to the SAP version 4.0 (26NOV2018) to be consistent with planned analysis.

Protocol Version # Date	SAP Section	Modification	Description and Rationale
5.0 08AUG2018	4.4	Added subject withdrawal due to non-compliance to the censoring rule. Added rules of missing dates imputation for partially missing AE onset, procedure, and initial replacement therapy dates.	Updated for clarifications and to reflect planned analysis for the study.
5.0 08AUG2018	6.1	Added subject withdrawal due to non-compliance to the censoring rule. Added hazard ratio margin calculation.	Updated for clarifications
5.0 08AUG2018	6.2	Deleted analysis for number of interventions needed to maintain patency prior to loss of primary assisted patency.	Removed to reflect planned analysis for the study.
5.0 08AUG2018	6.3	Added subject withdrawal due to non-compliance to the censoring rule.	Updated for clarifications
5.0 08AUG2018	7.2, 7.2.2, 7.2.4	Added the statement for imputing an AE start date if it was partially missing. Added the analysis for Sponsor assessed AE relationship to IMP and study procedure(s).	Updated for clarifications and to reflect planned analysis for the study.
5.0 08AUG2018	7.2.5	Removed the analysis for the relationship of the infection to the presence of access for dialysis other than study conduit.	Removed to reflect planned analysis for the study.

Protocol Version # Date	SAP Section	Modification	Description and Rationale
5.0 08AUG2018	7.2.6	Modified the language for aneurysms and pseudo-aneurysms analysis. Added analysis for thrombosis, stenosis and bleeding of study access	Updated for clarifications and to reflect planned analysis for the study.
5.0 08AUG2018	7.3	Removed PRA from the analysis	Removed to reflect planned analysis for the study.
5.0 08AUG2018	9	Added "if applicable" at the end of the sentence.	Updated for clarifications.

The table below details the changes made to the SAP version 5.0 (01May2019) to reflect the planned analysis for Month 24.

Protocol Version # Date	SAP Section	Modification	Description and Rationale
5.0 08AUG2018	6.1	Removed withdrawal due to non-compliance. Updated the language for non-inferiority hazard ratio margin calculation.	Updated for clarifications and to reflect planned analysis for the study.
5.0 08AUG2018	6.1.1	Added this section for Month 24 analysis.	Updated to reflect planned analysis for Month 24.

ABBREVIATIONS AND TERMS

Abbreviation or specialist term	Explanation
AE	Adverse event
ANSI	American National Standards Institute
AQL	Acceptable Quality Level
BMI	Body Mass Index
CDC	Center for Disease Control and Prevention
CEC	Clinical Events Committee
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
DMC	Data Monitoring Committee
DMP	Data Management Plan
eCRF	Electronic case report form
ePTFE	Expanded polytetrafluoroethylene
ESRD	End stage renal disease
HAV	Human acellular vessel (Note: was HAVG [Human Acellular Vascular Graft])
ICH	International Conference on Harmonization
IMP	Investigational medicinal product
INR	International normalized ratio
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
PP	Per-Protocol
PRA	Panel reactive antibody
PT	Prothrombin time

ABBREVIATIONS AND TERMS

Abbreviation or specialist term	Explanation
PT	Preferred Term
QC	Quality Control
RMST	Restricted Mean Survival Time
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
$spKt/V_{urea}$	Measure of dialysis adequacy for a single hemodialysis treatment using the single pooled method
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
USA	United States of America
USRDS	United States Renal Data System
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) is based on Humacyte Inc.'s Protocol # CLN-PRO-V006, titled "An Assessment of Humacyte's Human Acellular Vessel in Patients Needing Renal Preplacement Therapy: A Comparison with ePTFE Grafts as Conduits for Hemodialysis (HUMANITY)". See the study Protocol for details on study rationale, conduct and endpoints.

The purpose of this SAP is to provide details of the statistical analyses specified in the study protocol. The SAP summarizes key aspects of the study to provide context for statistical methods and presents details of the planned statistical methods addressing:

- The primary analysis after all subjects are at least 18 months post-implantation or censored for death, kidney transplant or withdrawal,
- A second analysis after all subjects are at least 24 months post-implantation or censored for death, kidney transplant or withdrawal, and
- A final analysis of the study after subjects with a patent conduit at 2 years (24 months) have completed 5 years (60 months) of follow-up after implantation, or until conduit abandonment.

This study will be conducted in compliance with the study protocol and ICH guideline E9 (Statistical Principles for Clinical Trials 1998).

2 OBJECTIVES AND ENDPOINTS

2.1 OBJECTIVES

Primary Efficacy Objective

To compare the Secondary Patency of the HAV with that of the ePTFE graft when used as a conduit for hemodialysis.

Secondary Objectives

2.1.0.1 *Key Secondary Efficacy Objective*

To compare the Primary Patency of the HAV with that of the ePTFE graft.

2.1.0.2 *Other Secondary Efficacy Objectives*

- To compare the rate of interventions needed to maintain/restore patency of the HAV with that of the ePTFE graft
- To compare the Primary Assisted Patency of the HAV with that of the ePTFE graft
- To describe the histopathological remodeling of samples from HAV and ePTFE grafts
- To compare the efficiency of dialysis with the HAV with that of the ePTFE graft in a subset of subjects

2.1.0.3 *Key Secondary Safety Objective*

- To compare the rate of access-related infections for the HAV with that of the ePTFE graft.

2.1.0.4 *Other Secondary Safety Objectives*

- To compare the safety and tolerability of the HAV with that of the ePTFE graft
- To compare the relative rates of true aneurysm and pseudo-aneurysm formation

2.2 ENDPOINTS

2.2.1. Primary Efficacy Endpoint

Time to loss of Secondary Patency from implantation. Secondary Patency is defined as 'the interval from the time of access placement until access abandonment', i.e., patent with or without interventions (Sidawy 2002). "Abandonment" is defined as no remaining segment of the study conduit remains incorporated into the vascular access circuit used for dialysis (conversely, if some portion of the study conduit is still being used for dialysis it is not considered abandoned).

2.2.2. Secondary Endpoints

2.2.0.1 *Key Secondary Efficacy Endpoint*

Time to loss of Primary Patency from implantation. Primary Patency is defined as 'the interval from the time of access placement until any intervention designed to maintain or reestablish patency, access thrombosis or the time of measurement of patency', i.e., patent without interventions (Sidawy 2002).

2.2.0.2 *Other Secondary Efficacy Endpoints*

- Rate of interventions required to achieve/maintain Secondary Patency
- Time to loss of Primary Assisted Patency from implantation. Primary Assisted Patency is defined as 'the interval from the time of access placement until access thrombosis or the time of measurement of patency, including intervening manipulations (surgical or endovascular interventions) designed to maintain the functionality of patent access' i.e., patent without an intervention to clear a thrombus (Sidawy 2002)
- Histopathological remodeling of any study conduit (based on samples collected)
- The efficiency of dialysis as assessed by spKt/Vurea (obtained from dialysis unit for a subset of subjects)

2.2.0.3 *Key Secondary Safety Endpoint*

Access-related infections (CDC 2013).

2.2.0.4 *Other Secondary Safety Endpoints*

- Frequency and severity of adverse events
- Study conduit dilatation:
    - True aneurysm formation (conduit lumen diameter > 9mm)
    - Pseudo-aneurysm formation
- Study conduit spontaneous rupture
- Anastomotic bleeding or spontaneous rupture

2.2.0.5 *Events of Special Interest*

Events of special interest related to interventions and infections will be evaluated and include the following:

- Study conduit abandonment
- Thrombosis/ thrombectomy
- Angioplasty or stenting
- Access-related infection

- Pseudo-aneurysm or true aneurysm (conduit lumen diameter > 9mm) formation
- Study conduit spontaneous rupture
    - Iatrogenic injuries are not an Event of Special Interest and should be reported as an AE
- Revision or ligation of the study conduit
- Study conduit removal
- Steal syndrome

3 INVESTIGATIONAL PLAN

3.1 STUDY DESIGN

This is a prospective, multicenter, multinational, open-label, randomized, two-arm, comparative phase 3 study. Approximately 35 sites in the US, Europe and Israel are planned for the study. Subjects who continue to meet inclusion and exclusion criteria on the day of surgery will be randomized in a 1:1 ratio to receive either the HAV or the ePTFE graft during surgery. The randomization will use a block size of 4 subjects and will be stratified by the upper arm or fore-arm placement. Subjects are considered enrolled at the time of completed informed consent. At least 350 subjects with implanted study conduits [175 with Human Acellular Vessel (HAV), 175 with an expanded polytetrafluoroethylene graft (ePTFE)] are planned to be enrolled in the study.

All enrolled subjects will be followed by study specific visits until the subject completes 2 years (24 months) of follow-up after implantation (irrespective of patency status).

After 2 years, only subjects with a patent conduit will continue to be followed (while the study conduit remains patent) for up to 5 years (60 months) post-implantation or until conduit abandonment (loss of Secondary Patency) at routine study visits. The expected duration of the clinical investigation is 76 months from the initiation of enrollment through the completion of data collection. See Appendix 1 of the study protocol for details of the schedule assessments.

A Data Monitoring Committee (DMC) will be established to review safety on an ongoing basis and to provide recommendations about stopping, continuing or otherwise modifying the study. The DMC will review data unblinded by treatment group and will consist of individuals who are not directly involved in the conduct of the study. As part of their oversight of study conduct, the DMC will review the pattern of interventions and abandonments between treatment groups overall and by study site to assess whether the management of access complications is similar in the two treatment groups.

A separate charter will be established that will describe the roles and responsibilities of the DMC. Responsibilities of the DMC will include review of aggregate safety data from other studies in the HAV clinical development program.

3.2 TREATMENT

This study compares a 6 mm diameter ePTFE graft (Gore® PROPATEN® Vascular Graft or Bard® Impra® Vascular Graft) with the Humacyte Human Acellular Vessel (HAV) in their use as conduits for vascular access. Selection of the ePTFE graft to be implanted in a subject randomized to the comparator arm will be made by the investigator from the two protocol-specified options.

3.2.1 Treatment Arm Assignment

At least 350 subjects who meet inclusion/exclusion criteria will be randomized in the study across multiple investigative sites. Study site personnel will randomize the subject utilizing a voice- or web-based randomization system to either HAV or ePTFE during surgery (i.e., after the surgical site [upper- vs fore-arm] has been selected and after confirmation that the subject is not a candidate for creation of an autologous AV fistula). Randomization may only occur once the arterial and venous exposures have been completed with confirmation of adequate arterial inflow and venous outflow. The randomization schema will ensure that subjects will be randomly assigned in a 1:1 ratio to the HAV or ePTFE arms of the study.

The randomization will be stratified by country (6 planned: US, Poland, Israel, Germany, UK and Portugal) and the upper arm or forearm placement based on the Investigator's determination of where the study conduit should be located. A blocked randomization of size 4 will be used. Subjects are considered enrolled at the time of completed informed consent. Country will not be included as a stratification variable for the statistical analysis for effect, but is only included in the randomization scheme to ensure a balance of treatment groups in each country.

Controlling against bias

This is an open-label, comparative study. It is not possible to blind the investigators or study subjects. Study endpoints will be determined by the clinical decisions of the investigators (except for study conduit revisions and access-related infections). To reduce the potential for bias a Clinical Events Committee (CEC) will:

- Prospectively provide to study sites a set of clinical guidelines for study conduit interventions and abandonment.
- Review individual study conduit interventions and abandonment in a blinded fashion to assess compliance with these guidelines.

- Adjudicate study conduit revisions to determine whether the original study conduit was still being used for dialysis.
- Adjudicate access-related infections using the Centers for Disease Control and Prevention (CDC) definitions for dialysis-associated infections (CDC 2013).

The outcome of these adjudications (i.e., those involving study conduit revisions and access-related infections) will be used as endpoints in the trial rather than the investigator determinations. All other study endpoints will be based on the clinical decisions of the investigators.

Additionally, cumulative event rates overall and by study arm will not be available to staff involved in the management of the study or study subject care.

Subject Compliance with IMP

Not Applicable

4 GENERAL CONSIDERATIONS FOR DATA ANALYSIS

Statistical analysis of data from this study will be the responsibility of CTI Clinical Trial & Consulting Services. Any change to the data analysis methods described in the protocol will require an amendment of this SAP only if it changes a principal feature of the protocol. Any other change to the data analysis methods that are described in the protocol, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Summaries and analyses will be performed by CTI Clinical Trial & Consulting Services and/or by Humacyte. Validated results will be reviewed by statisticians and clinicians at Humacyte for approval. For both safety and efficacy analyses, all analyses will be performed by treatment group (HAV, ePTFE graft). Subject listings of all data from the case report forms (CRFs) as well as any derived variables will be presented.

All analyses will be implemented using SAS Version 9.2 or more recent version.

The analyses for this study will be performed as follows:

- The primary analysis will be performed after all subjects are at least 18 months post-implantation and have completed the 18-month visit or have been censored for death, kidney transplant or withdrawal.
- A second analysis will be performed after all subjects are at least 24 months (2 years) post-implantation and have completed the 24-month visit or have been censored for death, kidney transplant or withdrawal.

- A final analysis will be performed after all subjects with a patent conduit at 2 years (24 months) have completed 5 years (60 months) of follow-up after implantation, or until conduit abandonment, if earlier.
- Additional ad hoc analyses may be performed as needed after the 24 month analyses.
- Interim safety and efficacy data will be provided periodically to the DMC as per the DMC Charter.

A hard database lock will be required for the data included in the planned primary (18 month) and second (24 month) analyses. Additional soft database locks may occur to support DMC activities. A final hard lock will be required for the final analysis.

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

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 and two-sided 95% confidence intervals (CI) will be calculated. All tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10, unless otherwise noted. Parametric and nonparametric methods, as determined by the distribution of each variable, will be used to test statistical hypotheses of continuous variables. In the event of highly skewed data, a logarithmic transformation will be considered prior to any statistical testing.

All p-values will be rounded to 3 decimal places. A p-value rounded to 1.000 will be displayed as >0.999, and a p-value rounded to 0.000 will be displayed as <0.001.

Multiplicity will be managed by testing the primary and key secondary endpoints in a hierarchical fashion. All analyses will be performed using data pooled across sites.

4.1 DATA AND PROGRAMMING QUALITY ASSURANCE

See Data Management Plan (DMP) for details on monitoring and source data verification.

Once all the source verification is complete, all queries are resolved, and the database has been updated appropriately, the database will be (hard or soft) locked and made available to CTI Biostatistics for analysis. Data may be pulled by CTI Biostatistics for DMC analyses at a time when source verification and query resolution is ongoing and the database is not locked. The DMC analyses may be performed by the CTI study statistician, but the results will not be disclosed to the sponsor.

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 different 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 primary analysis will be based on the Intent-to-Treat (ITT) analysis set defined as all randomized subjects (based on study conduit group assignment).

The following rules will apply to the ITT analysis set:

- Subjects in whom the wrong conduit is implanted (e.g. an HAV implanted in a subject randomized to an ePTFE graft) will be analyzed within their randomized group rather than in their implanted group
- Subjects in whom no study conduit was implanted will be considered as if abandoned on Day 0 and included in their randomized group
- Subjects in whom the site (upper vs forearm) of implantation is different from the intended site will be analyzed based on the intended site.

The analysis will be repeated using the modified Intent-to-Treat (mITT) analysis set defined as all subjects in whom a study conduit has been implanted (based on actual conduit implanted and the actual site).

A secondary analysis will be conducted in a Per Protocol (PP) analysis set defined as all subjects in whom a study conduit has been implanted (based on actual conduit implanted) and in whom there were no major protocol deviations or data integrity concerns.

Major protocol deviations will be reviewed and verified at the time of determination, the time between the database soft lock and hard lock. Humacyte will identify major protocol deviation categories prior to the close of the database for the primary, second and final analysis. An overall major protocol deviation listing will be reviewed just prior to database lock for final analysis. Humacyte will approve all final major protocol deviation determinations. The protocol deviations SAS dataset will then be generated but will not be entered into the database.

Safety analysis will be conducted using the safety analysis set, which is defined as all subjects who receive study treatment, with the subject's treatment group based on the treatment that was received.

4.3 ASSESSMENT WINDOWS

No analysis windows are planned for the study regarding data collected outside the protocol specified windows. All data will be included in the analysis based on the visit as it is recorded in the database.

4.4 HANDLING OF DROPOUTS OR MISSING DATA

The following rules will be used to handle the data for subjects who either died or withdrew for any other reason (had kidney transplant, lost to follow-up, subject decision, etc.) prior to the time of the efficacy analyses and therefore do not have data up to the time of the analyses:

- For the primary analysis, subjects who have patent study conduit at the time of death, kidney transplant, voluntary withdrawal or withdrawal due to non-compliance will be censored at that timepoint
- For the primary analysis, subjects who are lost to follow-up with a patent conduit will be censored at their last visit when it was known that the study conduit was patent
- For the primary analysis subjects lost to follow up whose study conduit was not patent at the last completed visit will be treated as abandoned at the time of study conduit occlusion
- A secondary analysis will be conducted following the rules above, except that death will be included as an event in conduit patency survival curves
- For dialysis efficiency, the most recent available data prior to the study visits will be used for the analysis
- No imputation for histology assessments. Data from histology assessments will be presented as is

No substitution of missing data will be used in laboratory measurements, vital signs, physical examinations and subject and graft status. In case of partially missing adverse event start dates, the start dates will be imputed by comparing to the implantation date of study conduit so that the corresponding AEs will be made treatment-emergent whenever possible, unless the available partial date information clearly indicates that the event happened before implantation. The general rule of imputation is to assign the first day of a month for a missing day and the first month of a year for a missing month when applicable. For interventions, if the date of a procedure has a missing day, the first day of that month will be assigned for the missing day unless the partial date has the same year and month as the implantation date, in which case, the day of the implantation will be assigned. For a partially missing initial renal replacement therapy date, the last day of the month will be assigned for the missing day and no imputation will be performed if both month and day are missing.

Data points that appear to be spurious will be investigated, and queried for possible resolution. Data points that are not resolved through queries will be included in the statistical analysis of the data as well as the data listings. Statistical analysis may also be performed with such apparently spurious data excluded as a sensitivity analysis to determine the impact of that data on the study results.

4.5 MULTIPLE COMPARISONS

Multiplicity for the primary and key secondary endpoints will be managed through a series of hypotheses presented in Section 6.2.

4.6 DATA DERIVATIONS AND TRANSFORMATIONS

The baseline value for a variable is defined as the last non-missing value for the variable prior to or at randomization/ (day of implant), unless otherwise specified.

5 STUDY SUBJECTS

At least 350 subjects who meet all inclusion/exclusion criteria will be randomized in the study across multiple investigative sites.

5.1 DISPOSITION OF SUBJECTS

Frequency counts and percentages of all subjects who are randomized and experience one of the following will be presented for each treatment group using the ITT analysis set:

- Conduit abandonment
- Death

For all subjects who discontinue from the study (or are censored), the reason for discontinuation will be reported by treatment group.

A subject listing for early discontinuations and reasons for discontinuation will be provided for the ITT analysis set.

5.2 PROTOCOL DEVIATIONS

The number and percent of subjects with major protocol deviations will be summarized using the ITT analysis set. See Section 4.2 for more details on protocol deviations.

A by-subject listing will be presented for subjects with major protocol deviations.

5.3 DEMOGRAPHIC CHARACTERISTICS

All demographic characteristics including gender, age (years), race/ethnicity, weight (kg), height (cm), etc. will be summarized using the ITT analysis set for each treatment group as well as for all subjects. Body mass index (BMI) will be calculated from available data:

$$\text{BMI} = [\text{Weight (kg)}] / [\text{Height (m}^2\text{)}]$$

Categorical variables will be summarized using frequencies and percentages and continuous measures will be summarized using the number of non-missing observations, mean, standard deviation, median, first and third quartiles, minimum and maximum. No formal hypothesis testing will be performed to compare differences in demographic characteristics between treatment groups. A by-subject demographic listing will be provided.

5.4 BASELINE CHARACTERISTICS

Baseline characteristics, including duration of end-stage renal disease, number of previous conduits placed with a description of what they were, etc. will be summarized using the ITT analysis set for each treatment group as well as for all subjects. Categorical variables will be summarized using frequencies and percentages and continuous measures will be summarized using the number of non-missing observations, mean, standard deviation, and possibly other descriptive statistics. No formal hypothesis testing will be performed to compare differences in baseline characteristics between treatment groups. A by-subject baseline characteristics listing will be provided.

5.5 MEDICAL HISTORY

A detailed medical history for each subject including the cause(s) of renal failure, history of dialysis and past vascular access procedures and smoking history will be obtained during screening. The number and percent of subjects with previous and active medical history at screening will be summarized and presented by body system using the ITT analysis set for each treatment group. A by-subject listing will also be created.

5.6 PRIOR AND CONCOMITANT MEDICATIONS

Prior medications are defined as all prescription medications plus aspirin taken within 7 days (whether continuing or not) prior to surgery (Day 0). Concomitant medications are defined as all prescription medications and aspirin taken at any time from Day 0 through the Month 24 visit. All prior and concomitant medications (including immediately pre-surgery and post-surgery medications) must be listed in the subject's medical record and recorded in the eCRF. Medications

used during anesthesia should be recorded in the anesthesia records but should not be transcribed in the eCRF. Medications used during anesthesia will not be included in any listings.

Prior and concomitant medications will be classified according to the most recent World Health Organization (WHO) drug dictionary available at the time of analysis. Prior and concomitant medications will be summarized using frequency and percentage by default Anatomical, Therapeutic, and Chemical (ATC) class, Preferred Term (PT) and treatment group using the ITT analysis set.

All concomitant medication data will be listed, sorted by treatment group, subject number, start and stop date. For antibiotics, the listing will also include medication generic name/components of combination product, indication, dose, frequency and route of administration.

6 EFFICACY ANALYSIS

6.1 PRIMARY EFFICACY ENDPOINT AND ANALYSIS

The primary efficacy endpoint is the time to loss of Secondary Patency assessed when all patients are at least 18 months after implantation (or have been censored). The primary analysis will be non-inferiority analysis using the following censoring rules:

- Subjects who have patent study conduits at the time of death, kidney transplant, voluntary withdrawal will be censored at that timepoint
- Subjects who are lost to follow-up will be censored at their last visit when it was known that the study conduit was patent
- Subjects who are lost to follow up and whose study conduit was not patent at the last completed visit will be treated as abandoned at the time of study conduit occlusion
- Subjects in whom a delayed decision is made to abandon the study conduit (e.g. delayed and then failed thrombectomy) will have the date of abandonment set as the date of the initial recognition of the thrombosis, not the date that a final decision is made
- For subjects who discontinue early or who complete without meeting criteria for the event, the time-to-event will be censored and defined as the number of days from randomization to the subject's last visit during the study

These censoring rules will apply to all 'time to' analyses. Subjects with End Stage Renal Disease (ESRD) have significant co-morbidities, with an annual death rate of ~20% (USRDS). Given the nature of the investigational product and the clinical setting, it is unlikely that the investigational product will be a causative factor in the overall death rate, and it is likely that the non-product related death rate will be similar in the two arms. For this reason, the primary analysis of Primary and Secondary Patency will censor deaths. However, a secondary analysis will be conducted in

which death is included as an event in the patency survival curves, to provide re-assurance that death does not modify the outcome of the trial.

The hazard ratio (HAV relative to ePTFE graft) will be estimated using a Cox proportional hazards regression with treatment group and the surgical placement stratification variable as factors. Based on the estimated event-free rate in the ePTFE graft arm at the data cut-off using Kaplan-Meier method, the non-inferiority margin will be determined by the hazard ratio corresponding to a difference of 10 percentage points. Hazard Ratio (HAV to ePTFE) Margin =Log(ePTFE K-M estimated event free rate - 0.1)/ Log(ePTFE K-M estimated event free rate). For analyses conducted at 12 months, the hazard ratio will be calculated from the ePTFE K-M estimated event-free rate at 12 months. For analyses conducted at 18 months, the hazard ratio will be calculated from the ePTFE K-M estimated event-free rate at 18 months. Similarly, for analyses conducted at 24 months, the hazard ratio will be calculated from the ePTFE K-M estimated event-free rate at 24 months. If the upper limit of the two-sided 95% confidence interval for the hazard ratio is less than the corresponding non-inferiority margin hazard ratio, then non-inferiority will be demonstrated.

The primary analysis will be in the ITT analysis set. The analysis of the primary endpoints of interest will be repeated using the mITT and per-protocol analyses sets as confirmatory.

6.1.1 EFFICACY ANALYSIS AT 24 MONTHS

The efficacy endpoint is the time to loss of Secondary Patency assessed when all patients are at least 24 months after implantation (or have been censored). The analysis at 24 months will be non-inferiority analysis using the following censoring rules:

- Subjects who have patent study conduits at the time of death, kidney transplant, voluntary withdrawal will be censored at that timepoint
- Subjects who have an abandonment of the study conduit due to improved health that leads to dialysis discontinuation will be censored at the date of abandonment
- Subjects who are lost to follow-up will be censored at their last visit when it was known that the study conduit was patent
- Subjects who are lost to follow up and whose study conduit was not patent at the last completed visit will be treated as abandoned at the time of study conduit occlusion
- Subjects in whom a delayed decision is made to abandon the study conduit (e.g. delayed and then failed thrombectomy) will have the date of abandonment set as the date of the initial recognition of the thrombosis, not the date that a final decision is made
- For subjects who discontinue early or who complete without meeting criteria for the event, the time-to-event will be censored and defined as the number of days from randomization to the subject's last visit during the study

At 24 months, the Restricted Mean Survival Time (RMST) method will be used to evaluate non-inferiority of HAV versus ePTFE for all non-censored subjects in the trial reaching 24 months. The RMST test is commonly employed in the setting of non-proportional hazards. It is well-established that the RMST has greater statistical power than the Cox hazard ratio model when proportionality is violated. (Kaur, 2018). We will utilize the 730.3 day timepoint (2 years, or 24 months), to calculate the mean survival times (loss of secondary patency) for each treatment group. The Weibull survival model will be first fit to the ePTFE time to loss of secondary patency event times to estimate the shape and scale parameters. These parameter estimates will then be used to derive the non-inferiority margin for the difference in RMST in days between HAV and ePTFE at 24 months, based on the non-inferiority hazard ratio margin determined by the method described above in Section 6.1.

At 24 months, additional efficacy analyses will be performed as follows:

a. The RMST method will be used to evaluate non-inferiority of HAV versus ePTFE for all non-censored subjects in the trial reaching 18 months. We will utilize the 18-month (547.9 days) timepoint to calculate the mean survival times (loss of secondary patency) for each treatment group.

b. The RMST method will be used to evaluate non-inferiority of HAV versus ePTFE for all non-censored subjects in the trial reaching 12 months. We will utilize the 12-month (365.25 days) timepoint to calculate the mean survival times (loss of secondary patency) for each cohort.

c. The RMST method will be used to evaluate non-inferiority of HAV versus ePTFE for all non-censored FEMALE subjects in the trial reaching 24 months.

d. The RMST method will be used to evaluate non-inferiority of HAV versus ePTFE for all non-censored MALE subjects in the trial reaching 24 months.

e. The RMST method will be used to evaluate non-inferiority of HAV versus ePTFE for all non-censored FEMALE subjects in the trial reaching 18 months.

f. The RMST method will be used to evaluate non-inferiority of HAV versus ePTFE for all non-censored MALE subjects in the trial reaching 18 months.

g. The hazard ratio (HAV relative to ePTFE graft) will be estimated using a Cox proportional hazards regression at 24 months, with right-censoring of data occurring after 24 months (Day 730). Based on the estimated event-free rate in the ePTFE graft arm at the data cut-off using Kaplan-Meier method, the non-inferiority margin will be determined by the hazard ratio corresponding to a difference of 10 percentage points. Hazard Ratio (HAV to ePTFE) Margin =Log(ePTFE K-M estimated event free rate – 0.1)/ Log(ePTFE K-M estimated event free rate). If the upper limit of the two-sided 95% confidence interval for

the hazard ratio is less than the corresponding non-inferiority margin hazard ratio, then non-inferiority will be demonstrated.

h. The hazard ratio (HAV relative to ePTFE graft) will be estimated for all FEMALE subjects using a Cox proportional hazards regression at 24 months, with right-censoring of data occurring after 24 months (Day 730).

i. The hazard ratio (HAV relative to ePTFE graft) will be estimated for all MALE subjects using a Cox proportional hazards regression at 24 months, with right-censoring of data occurring after 24 months (Day 730).

j. The hazard ratio (HAV relative to ePTFE graft) will be estimated for all FEMALE subjects using a Cox proportional hazards regression at 24 months, WITHOUT right-censoring of data occurring after 24 months.

k. The hazard ratio (HAV relative to ePTFE graft) will be estimated for all MALE subjects using a Cox proportional hazards regression at 24 months, WITHOUT right-censoring of data occurring after 24 months.

The primary analysis will be in the ITT analysis set. The analysis of the primary endpoints of interest will be repeated using the mITT and per-protocol analyses sets as confirmatory if the mITT or the PP analysis set is different from the ITT analysis set.

6.2 SECONDARY EFFICACY ENDPOINTS AND ANALYSES

If the primary efficacy analysis demonstrates non-inferiority, the following key secondary efficacy analyses will be performed at the same timepoint in the ITT analysis set using a fixed sequence testing procedure to control the overall level of significance. Thus, the results of a given key secondary analysis will be considered confirmatory only if the results of all previous tests are successful based on the use of a two-sided test at the alpha=0.05 level of significance. However, once a non-successful result is obtained, all subsequent results will be considered as exploratory rather than confirmatory. The key secondary analyses are the following:

- Superiority analysis of the time to loss of Secondary Patency using the same statistical approach as specified for the primary analysis, except that a two-sided superiority test will be performed,
- Non-inferiority analysis of the time to loss of Primary Patency using the same statistical approach and non-inferiority margin as specified for the primary analysis, and
- Superiority analysis of the time to loss of Primary Patency using the same statistical approach as specified for the primary analysis, except that a two-sided superiority test will be performed.

In order to provide descriptive summary statistics that are of interest, point estimates and 95% confidence intervals for patency (Primary, Primary Assisted and Secondary) survival probabilities will be provided for each group at 6, 12, 18, and 24 months. These estimates will be computed from Kaplan-Meier survival curves for each treatment group for each of the endpoints. For subjects who discontinue early or who complete without meeting criteria for the event, the time-to-event will be censored and defined as the number of days from randomization to the subject's last visit during the study.

Other secondary endpoints to be analyzed include:

- Interventions required that successfully achieved/maintained Secondary Patency. Interventions include whatever is done at one session. For example, thrombectomy + angioplasty at one session would be considered as 1 intervention. Summaries will include:
    - Proportion of subjects who had at least one intervention
    - Number of interventions per subject
    - Distribution of how many had 1, 2, 3… interventions
    - Rate of interventions defined as the number of interventions per subject per year while the conduit is patent (i.e. has not been abandoned). Results will be provided for Day 0 to Month 18 and overall (Day 0 to total follow-up period). Intervention rate for each 6-month interval will be reported.
    - The rate of interventions (number of interventions per 100 person-years) in the two arms will be compared using a Poisson regression model with treatment group and the surgical placement stratification variable as factors, if no overdispersion is present. Otherwise, a negative binomial regression will be used to adjust for overdispersion.
    - The number and rate of thrombectomies, angioplasties and revisions will be analyzed separately
- Interventions that failed to maintain/restore Secondary Patency. In the case when a delayed decision is made to abandon the study conduit (e.g. delayed and then failed thrombectomy), the date of abandonment is back dated to the initial recognition of the thrombosis. Any interventions performed after this date of abandonment will then be considered to have failed to maintain/restore Secondary Patency. Summaries for these interventions will include:
    - Proportion of subjects who had at least one failed intervention
    - Number of failed interventions per subject
    - Distribution of how many had 1, 2, 3 … failed interventions

- Superiority analysis of the time to loss of Primary Assisted Patency using log-rank test at the 0.05 significance level and similar censoring rules discussed for the primary endpoint.
- Histology assessments of any conduits will be summarized descriptively. Summaries will include the following:
    - The proportion of subjects in whom a sample has been collected
    - The histological findings in each arm will be described and listed
- Dialysis efficiency as assessed by spKt/Vurea (obtained from dialysis unit for a subset of subjects) will be summarized descriptively. The most recent available data prior to the study visits will be used for the analysis.

All secondary endpoints will be summarized by treatment group using counts and percentages for the categorical variables, and n, mean, median, standard deviations, minimum and maximum for the continuous endpoints.

All secondary analyses will occur after all subjects complete at least 18 months post implantation.

6.3 SENSITIVITY ANALYSES OF TIME TO LOSS OF SECONDARY PATENCY AND TIME TO LOSS OF PRIMARY PATENCY

Several sensitivity analyses of the primary endpoint (time to loss of secondary patency) and key secondary endpoint (time to loss of primary patency) will be conducted. Each of these analyses will be conducted using the same statistical methodology as described in Sections 6.1 and 6.2. The sensitivity analyses are described below, in terms of the changes that will be made to the descriptions provided in Sections 6.1 and 6.2. Sensitivity analyses being conducted to exclude subjects from the Ladenheim site are due to major GCP violations and data integrity concerns.

1. Exclude all subjects from the Ladenheim site.
2. Treat death as an event, but censor for transplant, lost to follow-up, withdrawal due to non-compliance and voluntary withdrawal.
3. Exclude all subjects from the Ladenheim site. Treat death as an event, but censor for transplant, lost to follow-up, withdrawal due to non-compliance and voluntary withdrawal.
4. Treat death, transplant, lost to follow-up, withdrawal due to non-compliance and voluntary withdrawal as an event.
5. Exclude all subjects from the Ladenheim site. Treat death, transplant, lost to follow-up, withdrawal due to non-compliance and voluntary withdrawal as an event.

The results of all sensitivity analyses will be reported without adjustment for multiplicity.

6.4 TERTIARY EFFICACY ENDPOINTS AND ANALYSES

No tertiary endpoints and/or analysis are planned for this study.

6.5 PROGNOSTIC FACTORS AND SUBGROUP ANALYSES

No analyses based on prognostic factors are planned for the study. Sub-group analysis by geographic region (USA versus non-USA), gender, race (White; non-White), ethnicity (Hispanic or Latino; non-Hispanic or Latino) actual surgical location (upper arm; forearm), age group (<55; >=55 and <=70; >70), BMI (<30; >=30) will be performed. The subgroup analyses will be performed by repeating the statistical methods described above for loss of secondary patency and loss of primary patency for each subgroup, except that the models will be adjusted by the actual surgical placement location (upper arm, forearm). For example, the models will be performed including only male subjects, and then will be repeated including only female subjects.

6.6 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not Applicable

7 SAFETY ANALYSIS

Safety assessments will include clinical chemistry, hematology, coagulation (prothrombin time or International Normalized Ratio (INR)), PRA, vital signs, adverse events, symptom directed physical exams and Duplex ultrasound assessments. Summaries of all safety assessments will be reported by visits where data are collected.

7.1 EXTENT OF EXPOSURE

There are two exposures that will be summarized:

1. Subject exposure during the study period is defined as the length of time from implant to death or early termination (e.g. lost to follow up, withdrew consent etc.).
2. Subject exposure to a patent conduit used for hemodialysis is defined as the length of time from first cannulation to explant, abandonment, death, transplant or early termination (e.g. lost to follow up, withdrew consent etc.).

Subject exposure during the study period and exposure to a patent study conduit used for hemodialysis will be reported by study arm at each analysis time point. Descriptive statistics will be provided for days of exposure. Overall exposure will be summarized in total subject-years. This will be calculated as follows:

Exposure in subject-years = Sum of duration of exposure in days (for all subjects in treatment group) / 365.25.

Frequency and percentages of subjects falling into the following different exposure ranges will also be summarized:

- >0 to =< 6 months (182 days),
- 6 months to =< 12 months (365 days),
- 12 months to =< 18 months (547 days),
- 18 months to =< 24 months (730 days),
- >24 months to =< 60 months (1825 days), and
- 60 months.

A listing of exposure data will be provided.

7.2 ADVERSE EVENTS

See the study protocol for the definition of adverse events (AE). The investigator's verbatim term for all adverse events will be mapped to System Organ Class (SOC) and preferred terms using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

From a technical regulatory perspective the HAV is a biologic medicinal product while the ePTFE graft is a device. For the purposes of this study and to allow for better cross-treatment arm comparisons of safety, and given that the IMP is a biologic drug, all events will be reported as if both arms were drugs.

AEs will be summarized as treatment-emergent AEs (TEAEs) for the Safety analysis set.

An AE will be considered a TEAE if the onset of the event is on or after the start of the anesthesia for the implant surgery. If an AE start date is completely missing, then the AE will be considered as TEAE unless it can be determined that the AE end date occurred prior to the anesthesia for the implant surgery. If the AE start date is partially missing then the start date will be imputed as described in Section 4.4.

7.2.1 Adverse Event Severity

See the study protocol for definition of adverse event severity grading levels.

Adverse Event Relationship to IMP

See the study protocol for definition of adverse event relationship to IMP. The relationship of an AE to IMP and study procedure will also be assessed by the sponsor. The sponsor assessment categories for relationship are unrelated/unlikely related or at least possibly related.

Serious Adverse Event

See the study protocol for definition of serious adverse event.

Adverse Events Summaries

An overall summary of all TEAEs will be presented overall and by treatment group and will include the following:

- the number and percentage of subjects experiencing a TEAE
- the number and percentage of subjects experiencing a TEAE by strongest relationship to IMP assessed by Principal Investigator and sponsor
- the number and percentage of subjects experiencing a TEAE by strongest relationship to study procedure(s) assessed by Principal Investigator and sponsor
- the number and percentage of subjects experiencing a TEAE by greatest intensity (see Section 9.3 of study protocol for details on intensity)
- the number and percentage of subjects experiencing a TEAE leading to IMP abandonment
- the number and percentage of subjects experiencing a treatment emergent SAE (TESAE)
- Deaths

In the overall summary of TEAEs table, besides tabulating the number and percentage of subjects, the total number of TEAE episodes will also be provided. If a subject has repeated episodes of a particular TEAE, all episodes will be counted in the summary table.

In addition to an overall summary, the following safety data with no inferential statistics will be provided:

- All Treatment Emergent AEs by SOC and PT
- All Serious AEs by SOC and PT
- All Treatment Emergent AEs leading to outcome of death by SOC and PT
- All Treatment Emergent AEs by SOC, PT and greatest severity
- All Treatment Emergent AEs by SOC, PT and greatest causal relationship to IMP and study procedure assessed by Principal Investigator and sponsor

- All Treatment Emergent AEs leading to study discontinuation by SOC and PT

For these summaries, if a subject has repeated events of a particular TEAE, only the most severe event or the event with the strongest causal relationship to IMP will be counted in the summary tables.

Access-Related Infections

In addition to the summaries indicated above in Section 7.2.4, the following access-related infection outputs are planned:

- Rate of access-related infections per 100 person-years of HAV/ePTFE graft use (i.e. censored at abandonment)
- Rate of access-related infections per 100 person-years over the 2-year post-implantation follow-up period

The analysis of access-related infections will be based on adjudicated events using a standardized definition of access-related infections. The infection rates will be compared using a Poisson regression model with treatment group and the surgical placement stratification variable as factors, if no overdispersion is present. Otherwise, a negative binomial regression will be used to adjust for overdispersion. The analysis will be conducted using a two-sided test at the alpha=0.05 level of significance. The following aspects associated with access-related infections will be described and summarized:

- The timing of first study access-related infection relative to the initiation of dialysis using the implanted conduit
- The use of intravenous antibiotics
- The need for hospitalization
- Other potential factors identified by the CEC

Events of Special Interest other than Access-Related Infections

Adverse events constituting or leading to events of special interest related to interventions and infections according to Section 2.2.2.5 will be presented descriptively. The analyses will include:

- Aneurysms: incidence rate of clinically significant (requiring intervention) and non-clinically significant (no interventions) aneurysms (100 person-years of retaining secondary patency since implantation) will be reported.

- Pseudo-aneurysms: incidence rate of clinically significant (requiring intervention) and non-clinically significant (no interventions) pseudo-aneurysms (100 person-years of HAV/ePTFE graft use since first cannulation) will be reported.
- Steal syndrome, thrombosis, stenosis, and bleeding of study access: Number and percent of subjects experiencing an event, events by severity, and events requiring interventions by severity will be tabulated by treatment group. Time to onset of first event will be presented descriptively.

All AEs and SAEs will be presented in individual listings. The listing will contain the following information: treatment group, verbatim term, SOC, PT, intensity, relationship to treatment, 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 a TEAE. Listings will be sorted by subject identification number, non-imputed 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

Data for clinical labs will be collected at screening, Day 28 (no prothrombin time (PT) or International Normalized Ratio (INR)), Months 6, 12, 18 and 24. Hematology and clinical chemistry, urine or serum pregnancy test and coagulation (PT or INR) samples will be analyzed at the study site's local laboratory. PRA samples will be collected during screening, Months 6, 12, 18 and 24 and early termination visits (for subjects who discontinue before Month 24 visit) and analyzed at a central laboratory.

Descriptive statistics by time of assessment will be presented for each laboratory parameter. Changes from baseline as well as shift tables will be presented. All laboratory values will be classified as low, normal, or high based on normal ranges supplied by each local laboratory. For purposes of analyses, laboratory results based upon standardized units will be used. Unscheduled visits and repeat measurements will be excluded from table summaries but will be included in data listings.

For each summary, the number of non-missing observations, mean, median, standard deviation, inter-quartile range, minimum, and maximum values will be presented by treatment. Individual clinical laboratory values (clinical chemistry, hematology, and urine or serum pregnancy test, coagulation) will be presented in subject data listings.

See the protocol for details on Laboratory testing on Clinical Chemistry, Hematology, Urine or Serum Pregnancy Test, Coagulation and PRA.

7.4 VITAL SIGNS

All vital sign measurements including temperature will be summarized by treatment group using descriptive statistics (n, mean, median, standard deviation, minimum and maximum). A listing of vital signs will also be reported.

7.5 PHYSICAL EXAMINATION

The number and percentage of subjects with relevant physical examination abnormalities at Screening will be summarized and presented for each body system. A listing of abnormalities will also be provided.

7.6 SUBJECT AND GRAFT STATUS

Summaries of subject status (alive or deceased), study conduit patency/usability, evidence of clinically significant aneurysm formation of the study conduit by clinical examination, need for interventions to maintain or restore patency of the study conduit and reasons for study conduit abandonment will be reported by frequency counts and percentages. Listings of the subject and graft status including the parameters provided above will be provided.

8 OTHER MEASURES

Summaries will be presented for Duplex ultrasound, dialysis and placement of a central venous catheter, time to first cannulation, clinical examination of conduit and interventions, surgical placement of conduit and documentation of any complications. All data indicated in this section, as well as vessel mapping data, will be listed.

9 CLINICAL EVENTS COMMITTEE ANALYSIS

Results from CEC assessment of compliances, CEC adjudication of study conduit revisions, and CEC adjudication of access-related infections will be summarized by country and by site if applicable.

10 INTERIM ANALYSIS

Not Applicable.

11 SAMPLE SIZE AND POWER CALCULATIONS

The original sample size calculation was based on the following assumptions:

For the primary endpoint of time to loss of Secondary Patency, the assumed 12-month event-free rates in the ePTFE graft is 60%. Based on 1:1 randomization, a 16-month enrollment period, and a 12-month follow-up period, a total sample size of 350 subjects will provide greater

- 90% power to demonstrate non-inferiority (with a 10% non-inferiority margin) if the 12-month event-free rate in the HAV arm is 66%
- 90% power to demonstrate superiority if the 12-month event-free rate in the HAV arm is 76%

For the key secondary endpoint of time to loss of Primary Patency, the assumed 6-month event-free rate in the ePTFE graft arm is 50%. Based on 1:1 randomization, a 16-month enrollment period, and a 12-month follow-up period, and under the assumption that the true 6-month event-free rate in the HAV arm is 55%, a total sample size of 350 subjects will provide greater than 90% power to demonstrate non-inferiority (assuming a non-inferiority margin of 10%). If the true rate in the HAV arm is as low as 53%, then there will be greater than 80% power to demonstrate non-inferiority.

During the course of the study a high enrolling site (~10% of total subjects) early terminated all of their remaining subjects and withdrew from study participation. The majority of these subjects had not yet had an event that would contribute to the primary endpoint analysis. To mitigate the potential loss of study power from this unexpected situation, the decision was made to extend the follow-up period for the primary and secondary efficacy analyses from 12 months post-implant to 18 months post-implant.

12 REFERENCES

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4. CDC. Dialysis Event Surveillance Manual. In: Network NHS, ed.: CDC; 2013.

13 APPENDICES

13.1 APPENDIX A: SCHEDULE OF STUDY PROCEDURES

See Study Protocol Appendix 1, pages 94 through 96 for details.

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Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
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Certified Delivered	Security Checked	9/22/2020 9:56:19 AM
Signing Complete	Security Checked	9/22/2020 9:57:23 AM
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