A Phase 2 Assessment of Humacyte's Human Acellular Vessel in Patients Needing Vascular Access for Dialysis

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STATISTICAL ANALYSIS PLAN

Version 1.0

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LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
ANSI	American National Standards Institute
AQL	Acceptable Quality Level
ATC	Anatomical, Therapeutic, and Chemical
BMI	Body Mass Index
CDA	Clinical Data Associate
CI	Confidence interval
CRF	Case report form
CVC	Central venous catheter
DMC	Data Monitoring Committee
eCRF	Electronic case report form
ET	Early termination
GCP	Good Clinical Practice
HAV	Human acellular vessel (Note: was HAVG [Human Acellular Vascular Graft])
HbA1c	Hemoglobin A1c
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IgG	Immunoglobulin G
IMP	Investigational medicinal product
INR	International normalized ratio
ITT	Intent-to-Treat
K-M	Kaplan Meier
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
PP	Per-Protocol
PRA	Panel reactive antibody
PT	Preferred Term
QC	Quality Control
RDC	Remote data capture
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) is based on Humacyte Inc.'s Protocol # CLN-PRO-V011, titled "A Phase 2 Assessment of Humacyte's Human Acellular Vessel in Patients Needing Vascular Access for Dialysis". 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 the last subject completes 3 months of follow up,
- A second analysis after all subjects have completed 12 months of follow up, and
- A final analysis of the study after the final subject completes 36 months follow up.

This study will be conducted in compliance with the study protocol and ICH guideline E9 [1] (Statistical Principles for Clinical Trials 1998).

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

To evaluate the safety, efficacy and immunogenicity over 3 months after implantation of HAVs manufactured using the commercial manufacturing system (LUNA).

2.1.2 Secondary Objectives

To evaluate the long-term safety and efficacy of the HAV (manufactured with the LUNA system) over a period of up to 36 months after implantation.

2.2 Endpoints

2.2.1 Primary Endpoints

2.2.1.1 Primary Safety Endpoints – assessed at 3 months post implantation

- Adverse events indicating possible mechanical failure or weakness of the HAV
    - Anastomotic rupture
    - Anastomotic bleeding
    - Spontaneous HAV rupture
    - Aneurysm
    - Pseudoaneurysm
    - Abnormal post cannulation hemostasis
- HAV infections
- Change from baseline of panel reactive antibody (PRA) and anti-HAV IgG levels (at 2

months)

- All adverse events (AEs)/serious adverse events (SAEs) and adverse events of special interest

2.2.1.2 Primary Efficacy Endpoints – assessed at 3 months post implantation

- Primary patency
    - Defined as being maintained until any intervention designed to maintain or reestablish patency, access thrombosis or the measurement of patency', i.e., patent without interventions
- Primary assisted patency
    - Defined as being maintained 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
- Secondary patency
    - Defined as being maintained until access abandonment
    - Access abandonment defined as no remaining segment of the study conduit is incorporated into the vascular access circuit used for dialysis

2.2.2 Secondary Endpoints

2.2.2.1 Secondary Safety Endpoints – assessed throughout the 36 months post implantation follow-up

- Adverse events indicating possible mechanical failure or weakness of the HAV
    - Anastomotic rupture
    - Anastomotic bleeding
    - Spontaneous HAV rupture
    - Aneurysm
    - Pseudoaneurysm
    - Abnormal post cannulation hemostasis
- HAV infections
- Change from baseline of PRA and anti-HAV IgG levels (at 12 months)
- All AEs/SAEs until 12 months post implant, after that only SAEs associated with the HAV and adverse events of special interest.

2.2.2.2 Secondary Efficacy Endpoints – assessed throughout the 36 months post implantation follow-up

- Primary patency

- Primary assisted patency
- Secondary patency
- Interventions required to achieve/maintain secondary patency
- Histopathological remodeling of any HAV (based on any samples collected)

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is a Phase 2, prospective, multicenter, open-label, single-arm study. Previous studies with the HAV have used Investigational Medicinal Product (IMP) manufactured using small-scale systems (Aura and Terra). Prior to commercialization, manufacturing has been switched to a larger-scale automated process with greater in-process controls (LUNA). Based on a large number of preclinical parameters, including those used for batch release, the IMP manufactured using the LUNA system is comparable to that used in earlier clinical studies. This study will allow confirmation of the short-term safety, efficacy and absence of immunogenicity of the LUNA product.

Up to 30 subjects who meet the inclusion/exclusion criteria specified in the Protocol, Section 5.1 will receive a HAV and will be followed to 12 months post-implantation at routine study visits regardless of patency status. After 12 months, subjects with a patent HAV will be followed (while the HAV remains patent) for up to 3 years (36 months) post-implantation at study visits every 6 months. See Appendix A for visit schedule.

3.2 Treatment

3.2.1 Randomization Scheme and Treatment Arm Assignment

This is a single-arm, open-label study. No randomization scheme or treatment arm assignment applies.

3.2.2 Blinding

This is an open-label study. Blinding of study subjects or study staff does not apply.

3.2.3 Dosing Schedule

The Humacyte HAV is a tissue-engineered vascular conduit for hemodialysis access. HAVs for this study will be manufactured using the LUNA commercial manufacturing system. Subjects will be implanted with an HAV in the forearm or upper arm using standard vascular surgical techniques on Day 1.

3.2.4 Subject Compliance with IMP

Not Applicable; the HAV is surgically implanted and remains *in situ* unless, in the judgment of the investigator, part or all of it requires explantation.

4. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

CTI Clinical Trial and Consulting Services will perform all efficacy and safety statistical analyses described in this SAP. 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.

The analyses for this study will be performed as follows:

- The primary analysis will be performed after the last subject completes 3 months of follow-up.
- A second analysis will be performed after all subjects have completed 12 months of follow-up.
- A final analysis will be performed after the last subject completes 36 months of follow-up.
- Interim safety data will be provided periodically to the Data Monitoring Committed (DMC) as per the DMC Charter.

A soft database lock will be required for the data included in the planned primary (3 months) and second (12 months) analyses. A final hard lock will be required for the final analysis at 36 months.

Statistical analyses will be primarily descriptive in nature. 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.

All tabulations will be based on pooled data across centers.

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

Subject data will be listed and sorted by subject number.

4.1 Data Quality Assurance

It is the responsibility of Humacyte or designee to perform auditing (if applicable) as part of implementing quality assurance. The purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate trial conduct and compliance with the protocol, SOPs, GCPs, and the applicable regulatory requirements. Authorized representatives from Humacyte, regulatory authorities and IEC will be granted access to the site and relevant study documentation to perform audits or inspections. The Principal Investigator (PI) should contact Humacyte immediately if contacted by a regulatory agency about an inspection involving this protocol.

A study coordinator at the study site will enter subject data into a remote data capture (RDC) database by completing eCRFs. All information recorded in the eCRFs for this study must be consistent with the investigator's source documentation for the study subjects. The study site will make available source documents to CTI personnel monitoring the study. The study monitor will verify consent of all subjects to participate in the study and will perform 100% source document

verification of the eCRF data.

A CTI Clinical Data Associate (CDA) will review the data for discrepancies via programmed electronic consistency checks, data listings, or manually. Any discrepancies discovered via the data review process will be issued as queries in the RDC system to the study site for resolution. Once all the source verification is complete, all queries are resolved, and the database has been updated appropriately, the database will be locked/frozen and made available to CTI Biostatistics for 3 months, 12 months, and final analyses.

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

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

At the time of analysis, a quality control (QC) review of database values listed in SAS output will be compared to the database. The sample size of fields to undergo QC review will be determined by utilizing American National Standards Institute (ANSI) sampling procedures [2]. 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 following three analysis sets will be defined for this study:

- Intent-to-Treat (ITT) set: The ITT set will include all enrolled subjects. The efficacy analysis will be based on the ITT set.
- Per Protocol (PP) set: The PP set is defined as all enrolled subjects in whom a HAV has been implanted and in whom there were no major protocol violations. Major protocol violations which would exclude a subject from the PP set will be defined by the sponsor prior to the database lock. Any protocol violation arising during the study which might have a substantial impact on the evaluation of efficacy or safety of HAV and which was not pre-specified as major, will be reviewed by Humacyte who will decide if the subject should be excluded from the PP set. If the number of subjects in the ITT set is different from that in the PP set, efficacy analysis on HAV patency will be repeated in the PP set.
- Safety analysis set: The Safety analysis set will include all enrolled subjects in whom a HAV has been implanted. The safety analysis will be conducted in the Safety analysis set.

4.3 Assessment Windows

For the purpose of listing and summarizing data, the time-in-study for each subject observation will be defined using study days. Such days will be calculated as follows:

- Date of assessment – date of HAV implantation + 1 for assessments done on or after date of HAV implantation
- Date of assessment – date of HAV implantation for assessments done before date of HAV implantation

Data will be summarized based on the eCRF study visit in which it was collected.

Baseline is defined as the last non-missing value prior to the HAV implantation.

If a repeat laboratory sample was drawn for a visit, the values from the repeat sample will be used for summary and analysis purposes. In this case, only the repeat sample values will be listed.

4.4 Handling of Dropouts or Missing Data

4.4.1 Time-to-Event Analyses

The following censoring rules will apply to all "time to event" analyses:

- Subjects who have patent HAV at the time of death, kidney transplant or withdrawal will be censored at that timepoint.
- Subjects who are lost to follow-up with a patent HAV will be censored at their last known visit.
- Subjects lost to follow up whose HAV was not patent at the last completed visit will be treated as abandoned at the time of HAV occlusion and recorded in the eCRFs.
- Subjects in whom a delayed decision is made to abandon the HAV (e.g. delayed and then failed thrombectomy) will have the date of abandonment recorded 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 at the subject's last date of study participation recorded in the eCRF disposition form.

4.4.2 Missing Data

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 HAV 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.

4.4.3 Spurious Data Points

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 Data Derivations and Transformations

Not applicable.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

A table of frequency counts and percentages of all enrolled subjects will be provided for the ITT set. Subject completion status and reasons for study discontinuation will be tabulated. A by-subject listing will be provided.

5.2 Protocol Deviations

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

5.3 Demographic Characteristics

Descriptive statistics will be used to summarize the demographic characteristics (gender, race, ethnicity, height (cm), weight (kg), and Body Mass Index (BMI) for the ITT set.

BMI = [Weight (kg)] / [Height (m^2)]

A by-subject listing of demographic characteristics will be provided.

5.4 Baseline Characteristics

Baseline characteristics including duration of end-stage disease, number and types of previous accesses, kidney transplant history, smoking history, etc. will be summarized for the ITT set using descriptive statistics. A by-subject listing will be presented.

5.5 Medical History

All medical conditions and procedures will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percent of subjects with each medical condition and surgical procedure will be presented for each SOC and PT using the ITT set.

5.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization (WHO) drug classifications. The number and percent of ITT subjects using prior and concomitant medications will be tabulated by Anatomical, Therapeutic, and Chemical (ATC) class and by preferred name. A listing of all medications recorded in the database will be provided.

6. EFFICACY ANALYSES

The status of Primary Patency, Primary Assisted Patency, and Secondary Patency will be assessed by the PI at Month 3, Month 12, and the end of the study. The patency status and the date of loss of patency will be recorded in the eCRF and used for the time-to-event analysis.

6.1 Primary Efficacy Endpoints and Analyses

The primary efficacy endpoints are the time to loss of Secondary Patency, Primary Patency, and Primary Assisted Patency when the last subject completes 3 months of follow-up. The analysis of primary efficacy endpoints will use the censoring rules described in Section 4.4.1.

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 using Kaplan-Meier (K-M) method.

The following K-M estimates will be provided:

- 25th, 50th (i.e., median) and 75th K-M percentiles with 95% Cis, if applicable
- Number and percent of subjects censored/not censored
- K-M estimates of the proportion of subjects with event-free

6.2 Secondary Efficacy Endpoints and Analyses

Secondary efficacy analyses on Primary/Primary Assisted/Secondary patency and intervention rate through 36 months of follow-up will be carried out on the ITT set.

The time to loss of Primary/Primary Assisted/Secondary patency will be analyzed by K-M method as described in Section 6.1. The K-M estimates of the proportion of subjects event-free at 6, 12, 24, and 36 months will be provided.

Interventions include whatever is done at one session. For example, thrombectomy + angioplasty at one session would be considered as one intervention. Summaries for interventions required that successfully achieved/maintained Secondary Patency will include:

- Number of interventions per subject
- Rate of interventions defined as the number of interventions per subject per year while the HAV is patent (i.e. has not been abandoned). Results will be provided for Day 0 to Month 12 and overall (Day 0 to total follow-up period).
- The number and percent of subjects with each of reasons for interventions
- The number and distribution of thrombectomies, angioplasties, stents, etc. will be analyzed separately

Analysis of histopathological remodeling of HAV will be performed by Humacyte.

6.3 Prognostic Factors and Subgroup Analyses

No analyses based on prognostic factors are planned for the study.

The following subgroup analyses will be performed:

- Primary, primary assisted, and secondary patency by gender.
- Primary, primary assisted, and secondary patency by study site.
- Total interventions by study site, and by gender.

The analysis listed above will be performed for each subgroup. For example, the K-M analysis will be performed including only male subjects, and then will be repeated including only female subjects.

7. SAFETY ANALYSIS

Safety data include results from laboratory testing (clinical chemistry, hematology, anti-HAV IgG antibodies, and PRA), adverse events, findings from symptom directed physical exams and Duplex ultrasound results. All safety summaries (or analyses if applicable) will be conducted using the Safety analysis set.

Screening laboratory testing will include International Normalized Ratio (INR) or Prothrombin time, and a serum or urine pregnancy dipstick test for women of childbearing potential in order to help ensure the eligibility and safety of prospective subjects.

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 explant, death or early termination (e.g. lost to follow up, withdrew consent etc.).

2. Subject exposure to a patent HAV 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 HAV used for hemodialysis will be reported 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 enrolled subjects) / 365.25.

7.2 Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered an IMP or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the IMP, whether or not related to the IMP.

During the Screening period (Day -45 to Day 0 prior to implantation), only SAEs related to study procedures will be reported beginning at the time the subject signs the informed consent form. From Day 0 after implantation to one-year post-implantation (Month 12 visit) or ET visit, whichever occurs earlier, all AEs will be reported.

During the long-term follow-up period from 1 year to 3 years post-implantation, only the following will be reported by the investigator:

- All related SAEs
- All Events of Special Interest as defined in Protocol Section 9.3

7.2.1 Treatment-emergent Adverse Events

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 4.4.2.

7.2.2 Adverse Event Severity

The severity of adverse events, including abnormal clinical laboratory values, will be assessed as 1-Mild, 2-Moderate, 3-Severe, 4-Life-threatening, and 5-Death. Refer to the study protocol Section 9.5 for criteria for defining the AE severity grades.

7.2.3 Adverse Event Relationship to HAV

Causal relationship assessment of an AE to the HAV and index surgical procedure are as following:

- Not Related

- Unlikely Related
- Possibly Related
- Definitely Related

Refer to study protocol, Section 9.4 for the criteria for determining causal relationship.

7.2.4 Serious Adverse Events

An AE is considered "serious" if, in the view of either the investigator or Sponsor, it:

- Results in death.
- Is Life-threatening.
- Results in persistent or significant disability/incapacity.
- Results in congenital anomaly or birth defect.
- Requires inpatient hospitalization or leads to prolongation of hospitalization.
- Represents a medically important event as determined by the investigator.

7.2.5 Adverse Event Summaries

All AEs (serious and non-serious) occurring following the HAV implantation, regardless of relationship to the IMP, will be included and classified by SOC and PT using the current MedDRA.

For TEAEs, the following will be summarized and presented for the Safety analysis set:

i. An overall summary of TEAEs, which includes:
    a. the number and percentage of subjects experiencing a TEAE
    b. the number and percentage of subjects experiencing a TEAE by strongest relationship to IMP
    c. the number and percentage of subjects experiencing a TEAE by strongest relationship to study procedure(s)
    d. the number and percentage of subjects experiencing a treatment emergent SAE (TESAE)
    e. the number and percentage of subjects experiencing a TEAE leading to outcome of death
ii. the number and percentage of subjects experiencing a TEAE by SOC and PT
iii. the number and percentage of subjects experiencing a TEAE by SOC, PT and the strongest relationship to IMP
iv. the number and percentage of subjects experiencing a TEAE by SOC, PT and the strongest relationship to study procedure(s)
v. the number and percentage of subjects experiencing a TESAE by SOC and PT
vi. the number and percentage of subjects experiencing a related TESAE by SOC and PT
vii. the number and percentage of subjects experiencing a TEAE leading to outcome of death

by SOC and PT

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

All occurrences of all AEs and SAEs will be listed for each subject. The listing will contain the following information: verbatim term, SOC, PT, severity, relationship to IMP and study procedure(s), date and day of onset, date and day of resolution/death, action/intervention taken (Yes/No), the outcome, whether the event was an SAE or AESI, whether it led to study withdrawal and whether it is a TEAE. Listings will be sorted by subject identification number, onset date, SOC, and PT. If the onset date is completely missing, then these events will be presented first.

7.2.6 Events of Special Interest

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

- HAV thrombosis: Number and percent of subjects experiencing the event, incidence rate of thrombosis (100 person-years of HAV exposure, censored at abandonment/renal transplant/early termination/death), and time from implantation to onset of the first event will be tabulated.
- HAV-related infection: Rate of HAV-related infections per100 person-years of HAV exposure (censored at abandonment/renal transplant/early termination/death), use of antibiotics, and the timing of first HAV-related infection relative to the initiation of dialysis using the HAV will be presented descriptively.
- Clinically significant (defined as severity of severe or greater, or requiring a surgical or radiological intervention) Stenosis of the HAV: Number and percent of subjects experiencing clinically significant stenosis, event rate (100 person-years of HAV exposure, censored at abandonment/renal transplant/early termination/death), event by severity, and time from implantation to onset of the first event will be reported.
- Treatment Emergent AEs leading to revision of the HAV by SOC and PT
- HAV spontaneous rupture, anastomotic bleeding, and anastomotic rupture: Number and percent of subjects experiencing the event, event by severity, and the time from implantation to onset of the first event will be tabulated.
- HAV aneurysm: Number and percent of subjects experiencing the event of interest, incidence rate of aneurysms (100 person-years of HAV exposure, censored at abandonment/renal transplant/early termination/death), and time from implantation to onset of the first event will be presented.
- HAV pseudo-aneurysm: Number and percent of subjects experiencing the event of interest, event rate (100 person-years of HAV exposure, censored at abandonment/renal transplant/early termination/death), and time from implantation to onset of the first event will be presented. Only clinically significant (defined as requiring a surgical or

radiological intervention to repair the pseudo-aneurysmal segment) HAV pseudo-aneurysm is considered as an event of special interest and will be continually recorded in the eCRFs during the long-term follow-up period from 1 year to 3 years post-implantation.

7.3 Clinical Laboratory Assessments

Blood samples will be collected for clinical chemistry and hematology testing at the following study visits: Screening, Day 28, and Months 2. In addition, laboratory testing at the Screening visit will include INR or Prothrombin time and a serum or urine pregnancy dipstick test for women of childbearing potential in order to help ensure the eligibility and safety of prospective subjects. Hematology and clinical chemistry, pregnancy test (serum or urine) and INR/ Prothrombin time samples will be analyzed at the study site's local laboratory. Blood samples will be collected for PRA/anti-HAV IgG analysis at the visits presented in Appendix A; these samples will be analyzed at a central laboratory.

Continuous clinical laboratory values will be summarized by presenting descriptive statistics of raw data and change from baseline values at each time point.

Laboratory parameter results from unscheduled visits will be excluded from table summaries but will be included in data listings.

Listings will include flags for values outside of the reference ranges, and clinical significance if a laboratory result is deemed abnormal.

7.4 Vital Signs

All vital sign measurements including resting blood pressure, heart rate and temperature will be summarized using descriptive statistics. A listing of vital signs will be reported.

7.5 Physical Examination

A listing of symptom-directed physical examination abnormalities will be provided.

7.6 Subject and Graft Status

Summaries of subject status (alive or deceased), HAV patency/usability, and reasons for HAV abandonment will be reported by frequency counts and percentages. Listings of the subject and HAV status will be provided.

7.7 Other Measures

Summaries will be presented, when deemed appropriate, for Duplex ultrasound, time to first cannulation, dialysis, kidney transplant during the study, clinical examination of access site and interventions, surgical placement of HAV and documentation of any complications. All data indicated in this section, as well as vessel mapping data, will be listed.

8. DATA MONITORING COMITTEE ANALYSES

An independent 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 consist of individuals who are not directly involved in the conduct of the

study. The DMC will review data from this study on an ongoing basis with the 1st scheduled DMC review after the last patient completes Month 3 and every 6 months thereafter. 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.

Prior to each DMC meeting, all available safety data will be extracted for the analysis. Data packages (tables, listings, figures) based on those data will be provided to the DMC for open and closed sessions in accordance with the DMC Charter.

9. SAMPLE SIZE DETERMINATION

This is an exploratory study with no formal hypothesis testing. No formal sample size estimates were performed. The number of subjects planned for this study is consistent with trials of this design and objectives.

10. REFERENCES

1. International conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Statistical principles for clinical trials (E9). International Conference of Harmonization. 1998
2. American National Standards Institute. Sampling Procedures and Tables for Inspection by Attributes, ANSI/ASQC Z1.4-1993

11. APPENDICES

11.1 Appendix A: Visit Schedule

	Screening D -45 to D 0	**D 0**	**D7[9]**	**D 28**	**M 2**	**M 3**	**M 6**	**M 12**	**M 18-36 at 6M intervals**	**ET[10]**
Visit Window	--	--	+8 D	±7 D	±7 D	±7 D	±14 D	±14 D	±1 M	--
Informed consent	X									
Demographics	X									
Medical history	X	X								
Concomitant medications[1]	X	X	X	X	X	X	X	X		X
Physical exam and temperature[2]	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
ECG (12-lead)	X									
Vessel mapping[3]	X									
Assessment of central vein stenosis	X									
Confirmation of eligibility (inclusion/exclusion criteria)[4]	X	X								
Surgical placement of HAV and documentation of any complications		X								
Labs[5]	X			X	X					
PRA / anti-HAV IgG	X			X	X		X	X		X
Assessment of surgical site healing			X	X						
Clinical examination of access site and HAV			X	X	X	X	X	X	X	X
Documentation of problems with access site and HAV and interventions			X	X	X	X	X	X	X	X

	Screening D -45 to D 0	**D 0**	**D7[9]**	**D 28**	**M 2**	**M 3**	**M 6**	**M 12**	**M 18-36 at 6M intervals**	**ET[10]**
Assessment of HAV Patency[6]		X	X	X	X	X	X	X	X	X
Duplex Ultrasound Examination				X	X	X	X	X	X	X
Determine suitability of HAV for dialysis[7]				X	X	X	X	X	X	
Document removal of pre-implantation CVC (if applicable)			X	X	X	X				X
Document hemodialysis / CVC use			X	X	X	X	X	X	X	X
Adverse Events / Events of Special Interest[8]	X	X	X	X	X	X	X	X	X	X

Abbreviations: D: day; M: Month; ECG: electrocardiogram; ET: early termination; PRA: panel reactive antibody; CVC: central venous catheter; IgG: Immunoglobulin G.

1: Record all prescription medications and aspirin the subject has taken in the 7 days prior to surgery (Day 0). At all other study visits, concomitant medications as well as aspirin taken during the study up to Month 12 will be recorded.

2: A complete PE will be performed at Screening, including height, weight, resting blood pressure and heart rate and temperature. Standard of care physical exams conducted prior to consent may be used for determination of eligibility provided they are within the screening period time window and all required data are available. Symptom-directed PEs will be conducted at all other study visits, as appropriate (denoted as (X)). Temperature should be obtained at all visits.

3: If adequate vessel mapping has been undertaken within the 8 weeks prior to the start of Screening and there has been no significant change in the condition of the subject (including insertion of CVC) then repeat vessel mapping is at the discretion of the Principal Investigator. Vessel mapping performed by ultrasound in the clinic by the investigator is acceptable.

4: After review by the Principal Investigator, the subject's Screening eCRFs will be provided to the Medical Monitor for review and confirmation of eligibility prior to implantation.

5: Labs include hematology and chemistry. Screening labs will also include INR (or Prothrombin time if INR value not available) and a serum or urine pregnancy dipstick test for women of childbearing potential. Standard of care laboratory evaluations conducted prior to consent may be used for determination of eligibility provided they are within the screening period time window.

6: Intraoperatively or immediately post-surgery and at Day 7-15, the investigator should use his/her preferred method to confirm patency and adequate flow in the HAV. At all other timepoints, duplex ultrasound will be used to assess patency, diameter of the lumen mid-conduit and flow rate and to monitor aneurysm development. After Month 12, a duplex ultrasound is to be performed at Month 24 and 36.

7: Beginning on Day 28, the investigator may evaluate the HAV to determine if it is suitable to be used for dialysis.

8: Only SAEs related to the screening procedures will be reported during the Screening period. All AEs will be reported from Day 0 after implantation up to the Month 12 visit. After the Month 12 visit up to Month 36, only the following will be reported by the investigator:

- All SAEs considered related to the HAV
- All Events of Special Interest.

9: Subjects will be assessed at a study visit that can occur anytime from Day 7 to 15.

10: Subjects withdrawn prior to the Month 36 visit will have ET assessments performed. Patients withdrawn prior to Month 12 should complete an ET that correlates with the procedures at Month 12. Patients withdrawn after Month 12 and prior to Month 36 should complete an ET visit that correlates with procedures post Month 12 through Month 36.