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

Medicinal Product:	Human Acellular Vessel (HAV)
Study No.:	CLN-PRO-V006
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IND No.:	15263
EudraCT No.:	2015-003261-28
Date:	08 August 2018
Version:	5.0

Confidentiality Statement

Statement of Compliance

This trial will be conducted in compliance with the protocol and the following regulatory and ethical requirements:

- Declaration of Helsinki adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, as last amended by the World Medical Assembly in 2013
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), E6 Good Clinical Practice: Consolidated Guidance (ICH E6)
- ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
- ICH E8 Guidance on General Considerations for Clinical Trials
- Applicable national and local regulatory requirements

Site Principal Investigator Agreement Page for the Protocol

Protocol Version 5.0 Dated: 08 August 2018

I agree:

- To assume responsibility for the proper conduct of the study at this site, and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by Humacyte Incorporated (Humacyte) or their authorized representatives.

- Not to implement any deviations from or changes to the protocol (including protocol amendments) without agreement from Humacyte and prior review and written approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and relevant regulatory authorities, if applicable) except where necessary to eliminate an immediate hazard to the subject(s), or for administrative aspects of the study (where permitted by all applicable regulatory requirements).

- That I am familiar with the appropriate use of the investigational medicinal product, as described in this protocol and any other information provided by Humacyte including, but not limited to the current Investigator Brochure or equivalent document.

- To ensure that all persons assisting me with the study are adequately informed about the investigational medicinal product and about their study-related duties and functions.

- That I have been informed that certain regulatory authorities require Humacyte to obtain and supply details about the investigator's ownership interest in Humacyte or the Investigational Medicinal Product, and more generally about his/her financial ties with Humacyte. Humacyte will use and disclose the information solely for the purpose of complying with regulatory requirements.

Principal Investigator: _____

Printed Name and Title

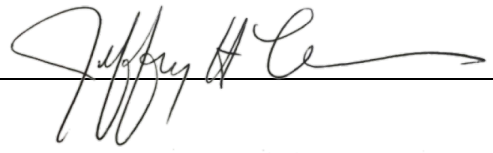
Signed: _____ Date: _____

Protocol Approval

Sponsor Medical Approval:

Jeffrey H. Lawson, MD, PhD

Chief Medical Officer, Humacyte, Inc.

Signed:  Date: 27Aug2018

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List of Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
AV	Arteriovenous
AVF	Autologous arteriovenous fistula
BUN	Blood urea nitrogen
CDC	Center for Disease Control and Prevention
CEC	Clinical Events Committee
CKD	Chronic kidney disease
CRO	Contract research organization
CVC	Central venous catheter
D	Day
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DTH	Delayed-type Hypersensitivity
ECG	Electrocardiogram
ECM	Extracellular Matrix
eCRF	Electronic case report form
ePTFE	Expanded polytetrafluoroethylene
ESA	Erythropoiesis-stimulating agent
ESRD	End-stage renal disease
ET	Early termination
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HAV	Human acellular vessel (note was HAVG [Human Acellular Vascular Graft])
HbA1c	Hemoglobin A1c
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethics committee
IgG	Immunoglobulin G
IMP	Investigational medicinal product

List of Abbreviations

IMPD	Investigational medicinal product dossier
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
LMWH	Low molecular weight heparin
M	Month
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
PAD	Peripheral arterial disease
PE	Physical examination
PHI	Protected health information
PP	Per Protocol
PRA	Panel reactive antibody
PT	Prothrombin time
PTFE	Polytetrafluoroethylene
RBC	Red blood cell
RRT	Renal replacement therapy
SAE	Serious adverse event
SOP	Standard operating procedure
$spKt/V_{urea}$	Measure of dialysis adequacy for a single hemodialysis treatment using the single pooled method
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper limit of normal
US	United States
WBC	White blood cell

Protocol Summary

Full Title	An Assessment of Humacyte's Human Acellular Vessel in Patients Needing Renal Replacement Therapy: A Comparison with ePTFE Grafts as Conduits for Hemodialysis (HUMANITY)
Clinical Trial Phase	Phase 3
Sponsor	Humacyte, Inc.
Planned Study Sites	Approximately 35 Sites in the US, Europe and Israel
Sample Size	At least 350 evaluable subjects with implanted study conduits; 175 with Human Acellular Vessel (HAV), 175 with an expanded polytetrafluoroethylene (ePTFE) graft
Expected Enrollment Start	2Q2016
Study Population	Subjects with end-stage renal disease (ESRD) who require hemodialysis and are targeted for implantation of an arteriovenous (AV) graft for dialysis access.
Enrollment Period	16 months
Study Duration	Each subject will be followed by study specific visits until he/she completes 2 years (24 months) of follow-up after implantation (irrespective of patency status). After 2 years, only subjects with a patent study conduit will be followed (while the study conduit remains patent) for up to 5 years (60 months) post-implantation at routine study visits. The expected duration of the clinical investigation is 76 months (initiation of enrollment through completion of data collection).
Study Design	Prospective, multicenter, multinational, open-label, randomized, two-arm, comparative study.
Investigational Device/Intervention Description	The Investigational Medicinal Product (IMP) is Humacyte's HAV, which is a tissue-engineered vascular conduit for hemodialysis access. The comparators are one of the following commercially available 6 mm ePTFE grafts: • Gore® PROPATEN® Vascular Graft (6mm x 40cm, straight, standard wall, non-stretch, non- tapered) • Bard® Impra® Vascular Graft (6mm x 40cm, straight, standard wall, non-stretch, non- tapered)

	Subjects will be implanted with either a HAV or an ePTFE graft in the forearm or upper arm using standard vascular surgical techniques. The randomization will occur during surgery and be 1:1 and stratified by upper arm or forearm placement based on the Principal Investigator's determination of where the study conduit should be located. All subjects will be required to take daily aspirin (75 to 325 mg) unless they are already taking another antiplatelet agent. Aspirin should be initiated no later than the day after surgical implantation of the study conduit (Day 1). If low molecular weight heparin (LMWH) is administered post-operatively, aspirin or other antiplatelet agent should be initiated after stopping LMWH. Subjects who are known to be aspirin-sensitive should take another antiplatelet agent at the discretion of the Principal Investigator.
Objectives	
Primary Objective	To compare the Secondary Patency of the HAV with that of the ePTFE graft when used as a conduit for hemodialysis.
Secondary Objectives	
Key Secondary Objectives	**Efficacy** To compare the Primary Patency of the HAV with that of the ePTFE graft. **Safety** To compare the rate of access-related infections for the HAV with that of the ePTFE graft.
Other Secondary Objectives	**Efficacy** 1. To compare the rate of interventions needed to maintain/restore patency of the HAV with that of the ePTFE graft. 2. To compare the Primary Assisted Patency of the HAV with that of the ePTFE graft. 3. To describe the histopathological remodeling of samples from HAVs and ePTFE grafts. 4. To compare the efficiency of dialysis with the HAV with that of

	the ePTFE graft in a subset of subjects. **Safety** 1. To compare the safety and tolerability of the HAV with that of the ePTFE graft. 2. To compare the relative rates of true aneurysm and pseudo-aneurysm formation.
Inclusion Criteria	1. Subjects with ESRD who are not, or who are no longer, candidates for creation of an autologous AV fistula and therefore need placement of an AV graft in the arm (upper- or forearm) to start or maintain hemodialysis therapy. 2. Either on hemodialysis or expected to start hemodialysis within 12 weeks of study conduit implantation. 3. At least 18 years of age at Screening. 4. Suitable anatomy for implantation of straight or looped conduits in either the forearm or upper arm (not crossing the elbow). 5. Hemoglobin ≥8 g/dL and platelet count ≥100,000 cells/mm^3 prior to Day 0 (within 35 days). 6. Other hematological and biochemical parameters within a range consistent with ESRD prior to Day 0 (within 35 days). 7. Adequate liver function prior to Day 0 (within 35 days), defined as both of the following: a. ≤2x upper limit of normal (ULN) for serum bilirubin, aspartate transaminase (AST), and alanine transaminase (ALT) b. ≤1.5 for International Normalized Ratio (INR) or prothrombin time (PT) ≤ 18 seconds unless the subject is taking an anticoagulant at the time 8. Female subjects must be either: a. Of non-childbearing potential, which is defined as post-menopausal (at least 1 year without menses prior to Screening) or documented surgically sterile or post hysterectomy (at least 1 month prior to Screening) b. Or, of childbearing potential, in which case: i. Must have a negative serum or urine

	pregnancy test at Screening, and ii. Must agree to use at least one form of the following birth control methods for the duration of the study: 1. Established use of oral, injectable or implanted hormonal methods of contraception 2. Placement of an intrauterine device or intrauterine system 3. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/ gel/ film/ cream/ suppository 9. Subject, or legal representative, able to communicate effectively with investigative staff, competent and willing to give written informed consent, and able to comply with entire study procedures including all scheduled follow-up visits. 10. Life expectancy of at least 1 year.
Exclusion Criteria	1. History or evidence of severe peripheral vascular disease in the intended arm for implantation. 2. Known or suspected central vein stenosis or conduit occlusion on the ipsilateral side of the planned implantation, unless the stenosis is corrected prior to study conduit implantation. 3. Treatment with any investigational drug or device within 60 days prior to study entry (Day 0) or ongoing participation in a clinical trial of an investigational product. 4. Cancer that is actively being treated with a cytotoxic agent. 5. Documented hyper-coagulable state. 6. Bleeding diathesis. 7. Active clinically significant immune-mediated disease, not controlled by maintenance immunosuppression. a. Low dose glucocorticoid therapy (e.g. up to 10mg a day prednisone or prednisolone) is acceptable. b. High dose glucocorticoid therapy for treatment of autoimmune flare, or other inflammatory diseases is excluded. c. Patients using glucocorticoids for

	immunosuppression post-transplant to prevent against transplanted allograft rejection in the period post allograft failure are excluded. d. The following examples of immunosuppressive agents (or the like) are exclusionary for enrollment in this clinical trial: i. tacrolimus or FK506 [Prograf] ii. mycophenolate mofetil [Cellcept], iii. cyclosporine [Sandimmune or Gengraf] iv. Sirolimus administered systemically (Sirolimus in drug eluting stents is NOT an exclusion) 8. Anticipated renal transplant within 6 months. 9. Venous outflow from study conduit cannot be placed more centrally than the venous outflow of any previous failed access in that extremity. 10. Active local or systemic infection (white blood cells [WBC] > 15,000 cells/mm^3 at Screening). If the infection resolves, the subject must be at least one week post resolution of that infection before implantation. 11. Known serious allergy to planned antiplatelet agent. 12. Pregnant women, or women intending to become pregnant during the course of the trial. 13. Any other condition which in the judgment of the investigator would preclude adequate evaluation of the safety and efficacy of the study conduit. 14. Previous enrollment in this study or any other study with the HAV. 15. Employees of Humacyte and employees or relatives of the investigator.
Criteria for Evaluation	
Primary Endpoint	Time to loss of Secondary Patency from implantation • Defined as 'the interval from the time of access placement until access abandonment', i.e., patent with or without interventions. (Sidawy 2002)
Secondary Endpoints	

Key Secondary Endpoints	**Efficacy** Time to loss of Primary Patency from implantation • 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). **Safety** Access-related infections (CDC 2013).

Other Secondary Endpoints	**Efficacy**
	• Rate of interventions required to achieve/maintain Secondary Patency.
	• Time to loss of Primary Assisted Patency from implantation.
	  ○ 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 any samples collected).
	• The efficiency of dialysis as assessed by spKt/V_{urea} (obtained from dialysis unit for a subset of subjects).
	Safety
	• Frequency and severity of adverse events (AEs)
	• Study conduit dilatation:
	  ○ True aneurysm formation (conduit lumen diameter > 9 mm)
	  ○ Pseudo-aneurysm formation
	• Study conduit spontaneous rupture
	• Anastomotic bleeding or spontaneous rupture

	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 >9 mm) 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
Data Analysis	
Populations	The Intent-to-Treat (ITT) population is defined as all randomized subjects (based on study conduit group assignment). The modified Intent-to-Treat (mITT) population is defined as all subjects in whom a study conduit has been implanted (based on actual conduit implanted). The Per Protocol (PP) population is 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 violations.
Primary Efficacy Analysis	The primary efficacy analysis will be a non-inferiority analysis, which will be conducted when all subjects are at least 18 months post-implantation. It will be conducted using the ITT population with confirmatory analyses in the mITT and PP populations. The following rules for the analysis will apply: • Subjects in whom the wrong study conduit was 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. The following censoring rules will apply to all 'time to' analyses: • Subjects who have patent study conduits at the time of death, kidney transplant or 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 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 was made. The hazard ratio (HAV relative to ePTFE) will be estimated using a Cox proportional hazards regression model with treatment group and the randomization stratification variable as factors. Based on the estimated 18-month event-free rate in the ePTFE arm, the non-inferiority margin will be determined by the hazard ratio corresponding to a difference of 10 percentage points. If the lower limit of the two-sided 95% confidence interval for the hazard ratio is greater than the corresponding non-inferiority bound, then non-inferiority will be demonstrated.
Secondary Efficacy Analyses	
Key Secondary Analysis Efficacy	If the primary efficacy analysis demonstrates non-inferiority, the following key secondary analyses will be completed at the same timepoint in the ITT population 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; • Non-inferiority analysis of the time to loss of Primary Patency; • Superiority analysis of the time to loss of Primary Patency. The non-inferiority analysis of time to loss of Primary Patency will be completed using the same statistical approach and non-inferiority margin as specified for the primary analysis. The superiority analyses will be completed using the same statistical model as described for the corresponding non-inferiority analysis. The two arms will be compared using a two-sided test at the alpha=0.05 level of significance. 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.
Key Secondary Analysis Safety	For each of the two treatment groups, the access-related infection rate will be computed in 2 ways: • Rate of access-related infections per 100 person-years of HAV/ePTFE use (i.e., censored at abandonment). • Rate of access-related infections per 100 person-years over the 2-year post-implantation follow-up period. These analyses will be based on adjudicated events using a standardized definition of access-related infections (CDC 2013). For each of the 2 definitions, the infection rates in the two arms will be compared using a Poisson regression model with treatment group and the randomization stratification variable as factors. This analysis will be conducted using a two-sided test at the alpha=0.05 level of significance.
Other Secondary Analysis Efficacy	In the primary and key secondary analyses of Primary Patency and Secondary Patency, death will be treated as a censored outcome. These analyses will be repeated as supportive analyses with death treated as an event. Additionally, a time to event analysis will be conducted for all censored subjects and any subjects who withdraw for any reason. All secondary efficacy analyses that are superiority comparisons will

	be carried out using two-sided tests at the alpha=0.05 level of significance, with no adjustment for multiplicity. The rates 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 randomization stratification variable as factors. Secondary endpoints that are defined as time-to-event variables will be summarized using the Kaplan-Meier method and analyzed using the log-rank test. Proportion endpoints will be analyzed using Pearson's chi-square test and all other quantitative endpoints will be analyzed using the two-sample t-test. Any analysis on histopathological remodeling of any study conduit will be descriptive only.
Other Secondary Analysis Safety	All other safety data will be described only (i.e., no inferential statistics).
Sample Size	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 rate in the ePTFE arm is 60%. Based on 1:1 randomization, an estimated 16-month enrollment period, and a 12-month follow-up period, a total sample size of 350 subjects will provide: • 90% power to demonstrate non-inferiority (non-inferiority margin=10%) 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 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. 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.
Data Monitoring Committee (DMC)	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. 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. Responsibilities of the DMC will include review of aggregate safety data from other studies in the HAV clinical development program. The DMC will consist of individuals who are not directly involved in the conduct of the study. A separate charter will be established that will describe the roles and responsibilities of the DMC.
Clinical Events Committee (CEC) (Adjudication Process)	A Clinical Events Committee (CEC) will be established to do the following: • Prospectively provide to study sites a set of clinical guidelines for study conduit interventions and abandonment. • Review study conduit interventions and abandonment in a blinded fashion to assess compliance with provided 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 CEC will consist of individuals who are not directly involved in the conduct of the study. A separate charter will be established that will describe the roles and responsibilities of the CEC.

Protocol Approval (Version and Date)	v5.0 08 August 2018

1. STUDY PERSONNEL

An updated list of all study personnel will be maintained by the Contract Research Organization (CRO). Substantial protocol amendments will not be required for staff changes at Humacyte, the CRO or the sites.

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Note: Medical Monitors for the study are available for time-sensitive discussions for the US and for Europe/Israel.

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2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 End Stage Renal Disease and its Management

Chronic kidney disease (CKD) is a serious and growing worldwide health problem. At the end of 2012, there were 26 million American adults with CKD, of these ~600,000 had End Stage Renal Disease (ESRD) and ~400,000 were receiving hemodialysis (National Kidney Foundation 2014). In Europe, there are approximately 780,000 patients on dialysis, with an expectation that this population will grow (ERA-EDTA Registry 2014). As patients with CKD progress to ESRD there is a need to consider renal replacement therapy (RRT). The first choice is usually a renal transplant, but this is not always available and many patients need to start dialysis – either peritoneal dialysis or hemodialysis.

Vascular access is a prerequisite for hemodialysis. It allows blood to be directed to an extracorporeal dialysis machine and returned to the patient. The commonly accepted standards for dialysis management urge providers to consider an autologous arteriovenous fistula (AVF) as the first line strategy for permanent hemodialysis access (National Kidney Foundation 2006). Unfortunately, not all patients are candidates for native fistulae and many require synthetic grafts for vascular access. In these cases synthetic vascular grafts are used; currently available synthetic grafts are typically made of materials such as polytetrafluoroethylene (PTFE).

However, synthetic grafts are subject to complications, often frequent, that limit their long-term utility. Typical complications include infections, which may necessitate their removal (Nassar 2001, Ryan 2004), and thrombosis, with or without stenosis associated with intimal hyperplasia, that necessitate interventions to remove the thrombus, with or without angioplasty to open associated stenosis (Haskal 2010, Roy-Chaudhury 2001). While highly variable, the published literature suggests that synthetic grafts may have a primary patency of ~60% after six months and even less later, with secondary patency of ~60% after 1 year (Dixon 2009, Huber 2003, Miller 2007).

Multiple biological alternatives to synthetic grafts have been studied for dialysis access, but results have been generally poor with a high risk of aneurysmal dilatation. Retained xenogeneic cellular remnants also have the potential for an induced immune response to implanted materials (Smith 2009).

If neither synthetic grafts nor biological alternatives are available, many patients are forced to rely on long-term central vein catheters (CVC) for vascular access; however, CVCs are

associated with a high potential for infection and shorter patient survival (Bray 2012, Thompson 2007).

There is, thus, a need for alternative conduits that more closely mimic human vascular tissue and thus might avoid, or reduce, complications while providing a more durable vascular access.

2.1.1 Humacyte Human Acellular Vessel

The investigational medicinal product (IMP) is Humacyte's Human Acellular Vessel (HAV), which is a tissue-engineered vascular conduit developed to provide an alternative to synthetic and autologous conduits for vascular access for dialysis.

The HAV is cultured from human aortic vascular smooth muscle cells, in a bioreactor that imparts arterial-like strain conditions on the growing cells. After an 8-week culture period, the tissue is decellularized, to produce the final HAV. It is a sterile, non-pyrogenic acellular tubular vessel composed, primarily, of human collagen types I and III plus other extracellular matrix (ECM) proteins, including fibronectin and vitronectin. The HAV is 6 mm in diameter and approximately 42 cm in length.

2.1.2 Comparator

The comparator in this study will be a 6 mm diameter expanded polytetrafluoroethylene (ePTFE) graft. The grafts to be used in the comparator arm will be one of the following (at the discretion of the Principal Investigator at each site):

- Gore® PROPATEN® Vascular Graft (6mm x 40cm, straight, standard wall, non-stretch, non-tapered)
- Bard® Impra® Vascular Graft (6mm x 40cm, straight, standard wall, non-stretch, non-tapered)

2.2 Summary of Human Acellular Vessel Nonclinical Studies

Humacyte conducted 13 nonclinical studies to evaluate the safety and functionality of the HAV. These studies assessed the HAV prototypes, the HAV and extracts of the ECM material.

A xenograft-primate model (immunosuppressive-free) was developed to assess the performance of the HAV implanted as an arterio-venous shunt. Two pilot studies and 2 definitive Good Laboratory Practice (GLP)-compliant studies were performed in baboons (n=14) to investigate the safety and functionality of the HAV. The first 2 animals had the HAV implanted in the abdomen; in the remaining 12 animals the HAVs were implanted in the upper arm. Shared objectives across these studies encompassed an assessment of potential local and systemic responses, patency, tolerability, physical and biological properties of the HAV or HAV-derived material and integration of the graft material with the host tissue after implantation periods of 1–

6 months. In addition, immunological studies were conducted to assess humoral and cellular immune reactions associated with the HAV.

Overall, the results showed that the HAV was safe and well tolerated. For the 12 baboons with the HAV implanted in the upper arm, with the exception of post-operative arm swelling and redness, as well as surgical incision perturbation by a few animals, no significant issues associated with implantation of the HAV were encountered. In addition, these animals maintained their body weight and showed no outward signs indicative of toxicity. Clinical chemistry and hematological findings showed no evidence of systemic toxicity. Liver, pancreas, and kidney function tests remained within normal ranges. Gross observations of the major and minor organs at necropsy indicated that, in general, there were no notable abnormalities or changes attributable to the test article, including the heart, spleen, liver, kidney, brain, and lung. In 4 animals, swollen and/or inflamed lymph nodes were observed. Histopathologic examination of the heart, liver, kidney, brain, and lung revealed no significant abnormalities. In cases where microscopic findings were observed, they were considered to be unrelated to the test article.

In general, the HAV functioned as intended. Assessments of performance included HAV puncture, angiography and ultrasound. Ultrasonography showed no wall thickening of the HAV during the study. Flow rates through the HAV were determined to be >300 mL/min, adequate for hemodialysis in humans. The overall assisted patency rate was approximately 80% (11/14 animals). The degree and aggressiveness of the intimal hyperplasia response, a major cause of failure for PTFE arteriovenous (AV) grafts, was insignificant. The HAV were accessed successfully with 16-22 gauge needles followed by a 5 French sheathed access catheter. Hemostasis was achieved with light pressure, typically in under 10 minutes. In the majority of animals, macroscopic examination of the HAV and associated vasculature at explant indicated that they were intact and were not dilated, constricted, calcified or aneurysmal. Enlargement of the outflow brachial vein, a typical response associated with the increased blood flow into the vein, was common. Scarring was not observed. Host tissue growth that resembled adventitia was evident around the exterior of the HAV. The HAV were measured for strength pre-implant and post-explant by a suture retention test. The HAV generally had increased suture retention values post-explant, most likely due to the host remodeling the graft with cells and native ECM. No evidence of systemic infection attributable to implantation of the HAV was observed in any of the animals. One HAV developed an aneurysm that was resected and did not harm the animal.

Microscopic analysis indicated that the HAV integrated with the host tissue. The cellular host response to the HAV demonstrated smooth muscle actin-positive cells within the vessel wall, endothelial cells lining the lumen, and an adventitial-like outer layer adjacent to the HAV similar to that of native blood vessels. Calcification was not observed. The HAV were therefore populated with cell types characteristic of healthy native vasculature. Immunostaining showed that collagen type I, collagen type III, and fibronectin within the vessel wall displayed a more organized structure with more circumferential alignment after 6 months. Additionally, collagen type I, glycosaminoglycans, and elastin deposition increased over this time period. The observed changes in organization and composition of ECM components indicated that, aided by

infiltration of host vascular cells, HAV were re-modeled *in vivo* in a manner that mimicked the dynamic re-modeling process of native blood vessels.

The HAV did not elicit biologically-significant humoral or cellular immune response. Analysis of panel reactive antibody (PRA) levels showed no increase for any animal, indicative that the HAV did not cause production of the anti-human antibodies measured by this assay. In an *in vitro* T-cell proliferation assay, low stimulation rates (3% to 17%; at or below that of negative control) were observed when buffy coat cells from each animal were cultured with HAV material. Increases in immunoglobulin G (IgG) titer to the ECM, defined as >25 fold titer increase over baseline, were observed in all study animals regardless of HAV functional outcome. In addition to the implant of the HAV test article, an additional test article consisting of a micronized extract of the HAV, as well as phosphate-buffered saline (negative control), were injected intra-dermally into the upper hip/thigh of all animals to monitor for the development of a delayed-type hypersensitivity (DTH) immune response. No DTH reactions were observed in any animals.

Biocompatibility assessments of the HAV ECM were conducted in accordance with internationally-recognized (International Organization for Standardization [ISO]) protocols for medical implants. The ECM was tested *in vivo* in rabbits (1 and 4-weeks, intramuscular implantation) and *in vitro* in a bacterial reverse mutation assay (Ames) and a cytotoxicity assay using mouse fibroblast cells. The ECM met all toxicological and biocompatibility requirements in the *in vivo* rabbit model and also tested negative for mutagenic and cytotoxic activity in the *in vitro* tests.

Further details on the nonclinical development program are presented in the Investigator Brochure.

2.3 Summary of Human Acellular Vessel Clinical Studies

There are three ongoing Phase 2 trials with the HAV; two studies in dialysis that have enrolled a total of 60 subjects and one in peripheral arterial disease (PAD) that has enrolled 20 subjects. More information on the clinical profile of the HAV in these ongoing studies is provided in the Investigator Brochure.

2.3.1 Experience in Dialysis Patients

Two clinical studies are ongoing in subjects with ESRD, one in Poland (CLN-PRO-V001) and one in the United States (US; CLN-PRO-V003); both recruited subjects not suitable for creation of an autologous AVF. Most had experienced previous vascular access procedures, in many cases multiple attempts including both AV fistulae and synthetic grafts.

Initially, the HAV was not used for hemodialysis cannulation before 8 weeks; an amendment to the Polish study protocol (after 30 subjects) shortened that restriction to 4 weeks without any problems. The primary objectives of these two studies are to evaluate safety and efficacy

(Primary and Secondary Patency) at 6 months. Secondary objectives include measurement of a panel of reactive antibodies (PRA) response plus a 2 year evaluation of patency and an assessment of the need for interventions to maintain/restore patency.

All subjects (n=60) have now completed at least 12 months since implantation (or had a censoring event). Together these two trials provide an average of 17.7 months (range 12 to >24 months) of follow-up in 60 subjects with thousands of hemodialysis sessions. Overall there are 81.6 years of follow-up across the 60 subjects. The mean number of previous access-surgeries was 4 (range 1-9).

When HAV thrombosis has occurred it has almost always been managed successfully, often allowing immediate resumption of dialysis without the need for the placement of a CVC. Regular ultrasound surveillance has demonstrated an absence of true aneurysms or dilatation and flow rates through the HAV more than sufficient to allow for effective dialysis. While there have been a few pseudo-aneurysms, there have been no true dilatations nor aneurysms or significant changes in vessel diameter indicative of weakening or structural degeneration.

Across the two studies, the product has generally been well tolerated and blood chemistry, hematology and coagulation data are not indicative of any HAV-associated toxicity. Immunogenic response to the HAV material has not been observed as demonstrated by a general lack of HAV-related change in PRA levels (Class I or II). Three subjects had elevations in their PRA levels: all 3 subjects had experienced one or more renal transplant failures; one subject recently; one subject developed septic shock about a month before the elevated value; and the third subject, who was severely debilitated with a decubitus ulcer, died approximately a month after HAV abandonment.

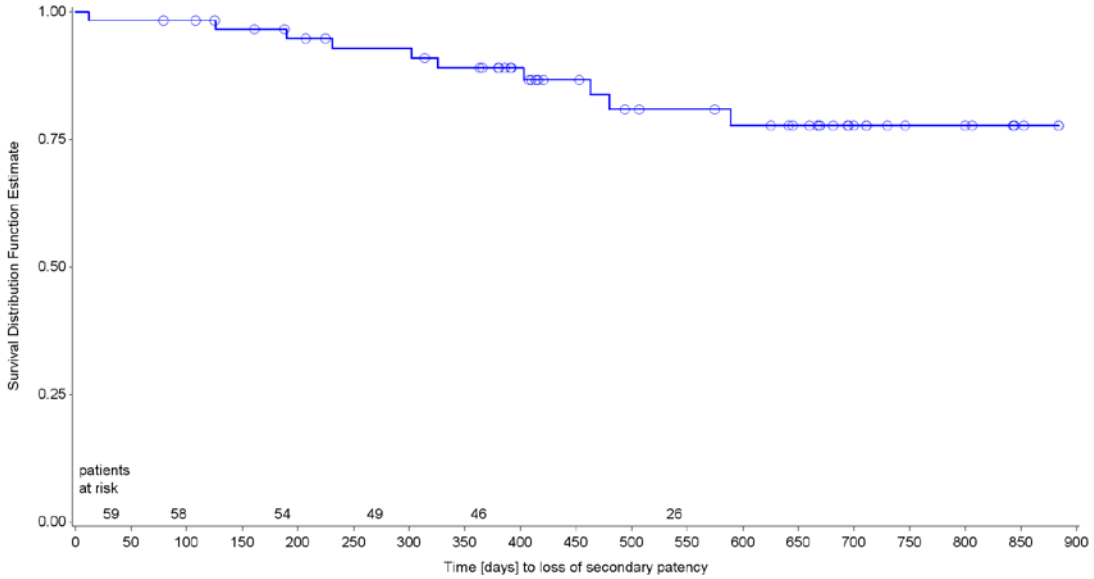
Immunoglobulin G (IgG) titers increased in 5 subjects; in 4 cases the IgG titer increased and then decreased while the HAV remained functional with no clinical evidence of an inflammatory response; in one case the IgG titer increase occurred in a subject who maintained Primary Patency.

Adverse events (AE) related to the HAV / access site (excluding thrombotic events) were few; there have been only three access-site infections, of which only one required removal of part of the HAV. There have been:

- 1 transplant (known to be functioning well at 12 months post-transplant)
- 4 deaths during follow-up and 2 deaths after abandonment; none of the deaths were considered related to the presence of the HAV

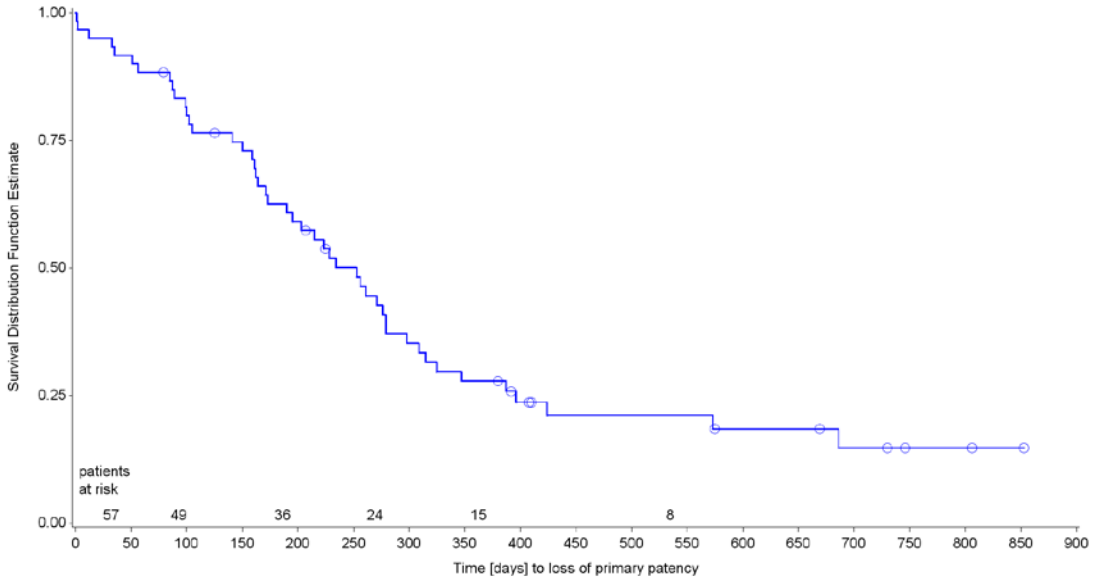
Across the two studies, Secondary Patency was 97% at 6 months, 89% at 12 months and 81% at 18 months (Figure 1); Primary Patency was 62% at 6 months and 28% at 12 months and 21% at 18 months (Figure 2).

Figure 1 Time to Loss of Patency-Pooled Data (CLN-PRO-V001 and CLN-PRO-V003) Kaplan-Meier Plot-Secondary Patency



Subjects at risk shown for the following key timepoints: Day 30, Day 90, Day 180, Day 270, Day 360, Day 540, i.e., Month 1, 3, 6, 9, 12, 18.
Subjects who discontinued early, died or were transplanted with the graft still patent, were censored at that timepoint.
Plot calculated 08 May 2015.

Figure 2 Time to Loss of Patency-Pooled Data (CLN-PRO-V001 and CLN-PRO-V003) Kaplan-Meier Plot-Primary Patency



Subjects at risk shown for the following key timepoints: Day 30, Day 90, Day 180, Day 270, Day 360, Day 540, i.e., Month 1, 3, 6, 9, 12, 18.
Subjects who discontinued early, died or were transplanted with the graft still patent, were censored at that timepoint.
Plot calculated 08 May 2015.

2.3.2 Human Acellular Vessel Host Response and Remodeling Data

Humacyte has been able to assess the general host response to the HAV in a number of human participants; this was accomplished through the microscopic examination of explanted HAV and adjoining tissue samples obtained during surgical revision procedures in eight cases. The analysis (mostly of a section close to the venous anastomosis) included assessments of:

- Cellular infiltration of histotypic, inflammatory and immunological populations.
- Extracellular remodeling processes, including neo-synthesis and reorganization of ECM components that typically occur in native blood vessels.

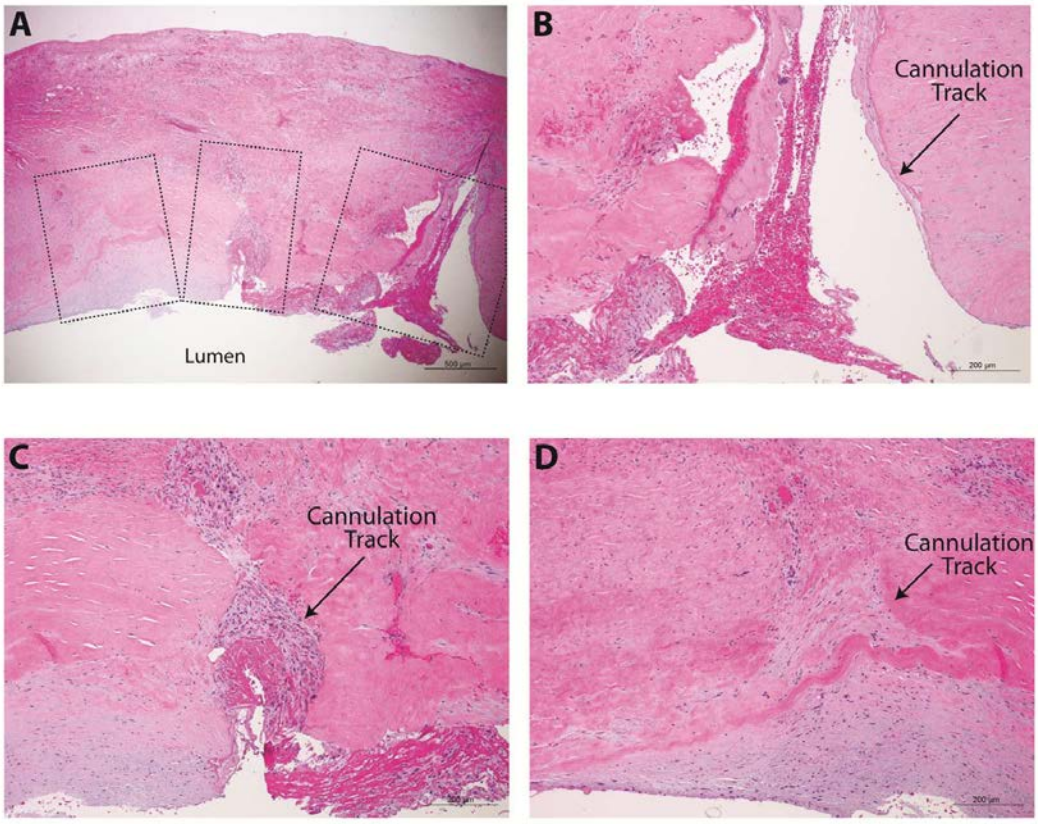
In these cases, small segments of the HAV and adjacent vascular tissue were explanted, fixed in formalin solution and shipped to Humacyte for analysis. Implant duration ranged from 16 to 55 weeks (median: 37 weeks).

In man, the HAV remodeled in a manner consistent with that observed in primate studies. There was infiltration of cell populations that are normally associated with angiogenesis and vascular organization and structure; namely, those with endothelial, smooth muscle and fibroblastic phenotypic characteristics were observed. Endothelial cells formed a monolayer on the luminal surface of the HAV. Migration of actin-positive smooth muscle cells into the wall of the HAV was consistently observed. A well-vascularized adventitial layer of non-constrictive fibrous tissue formed around HAV. Infiltration of the graft material by inflammatory and immunoreactive cell populations was either not evident or was mild and generally unremarkable. Degradation or breakdown of the implant was not observed.

Histotypic neo-synthesis and reorganization of the ECM was observed in patterns indicative of integration of the HAV into the host. An increase in the density of collagen type I, the main type of collagen found in the wall of native blood vessels, was apparent in the majority of HAV explant specimens. The structure of collagen type I in these specimens exhibited a more mature, organized pattern, with distinct fibers and a prominent circumferential alignment evident in explanted samples in comparison with pre-implant specimens. In some specimens, the fibrillar staining pattern of collagen III became more prominent and more organized, with a circumferential orientation. Fibronectin levels and staining patterns remained unchanged.

Cannulation sites within the HAV appeared to be repaired by the host in a fashion similar to wound repair in the body (Figure 3). In one case, an explanted specimen was tested for suture retention strength at the time of explant and exhibited a substantial increase over the pre-implant level.

Figure 3 Images of Mid-Vessel Segment Explanted at 11-Months Post-Implant



A: Low magnification showing 3 cannulation sites (in dashed boxes),
B: Fresh cannulation track,
C: Cannulation track during remodeling
D: Older cannulation track that has been repaired.
The images above show a mid-vessel segment explanted at 11 months post-implant, and shows several prior cannulation tracts from dialysis access. Section B shows a very recent cannulation site with fresh clot extending into the tract from the lumen. Sections C and D show partially healed cannulation tracts, with evidence of cellular repopulation extending in from the lumen. Remodeled cannulation tracks contain new collagen and a few micro-conduits.

In conclusion, the HAVs were remodeled by the host to form a vascular-like structure more similar to the histological appearance of native vasculature. The HAVs were repopulated by cell types that are characteristic of healthy native vasculature. Evidence of ECM remodeling processes, including neo-synthesis and reorganization of ECM components that typically occur in native blood vessels, were observed. The cellular infiltration and ECM remodeling patterns were indicative of the integration of the HAV into the host.

2.3.3 Experience in Peripheral Arterial Disease Patients

The safety and efficacy of HAV is currently being evaluated in a single group, uncontrolled, multicenter study. Eligible subjects required a femoro-popliteal bypass graft for the management of PAD. The patency of the graft after implantation is confirmed by intraoperative angiography or

ultrasound and subjects are followed out to 24 months. Twenty subjects have been enrolled; 19 have completed >6 months follow-up and 10 have completed ≥1 year; the mean follow-up is 11 months.

One subject died 19 days after HAV implantation, the death was considered unrelated to the HAV; five subjects have developed a thrombosis of the HAV.

2.4 Study Design Rationale

2.4.1 Study Population

The study is designed to recruit a broad range of ESRD patients in whom a clinical decision has been made to implant a 'graft' to provide vascular access for hemodialysis. Exclusion criteria have been restricted to those situations where use of an HAV or an ePTFE graft is likely to be inappropriate or to pose a potential risk to the study subject.

1. The trial is limited to adults because we do not believe that the diameter (6 mm) of the HAV is appropriate for children with smaller veins, especially if an anastomosis is placed distally in the arm to preserve vascular territory for future vascular access surgery. In addition, because the HAV does not stretch and it is unknown if it can extend to longer lengths after implantation, there could be a concern in children who are still growing.

2. Study subjects should be either on hemodialysis, or anticipated to start dialysis within 12 weeks of conduit implantation. This is to ensure that all subjects experience the regular needle insertions associated with hemodialysis and thus allowing us to evaluate in a comparative manner the integrity of the HAV in an appropriate clinical setting.

3. Subjects with documented bleeding or clotting problems are excluded because of general concerns with regard to these medical conditions in a trial related to the surgical placement of a vascular access, not because of investigational product-related concerns.

4. Subjects are excluded if they have insufficient arterial inflow or venous outflow, or any type of aberrant vascular anatomy that would preclude appropriate positioning of the HAV or the ePTFE graft.

5. Subjects are excluded if, in the opinion of the Principal Investigator, the subject has a life expectancy of less than a year. This will ensure that there is a significant opportunity for long-term follow-up to provide robust safety information.

2.4.2 Comparator Expanded Polytetrafluoroethylene Grafts

Currently, ePTFE is the most commonly implanted synthetic vascular graft material used for hemodialysis access. There is a wide range of commercially available ePTFE grafts. Because this trial will be conducted internationally (approximately 50% of subjects will be recruited in the United States [US] and 50% recruited in Europe / Israel), and because surgeon (Principal Investigator) preferences vary, the comparator arm will allow the individual surgeon to select from two of the most commonly used grafts:

- Gore® PROPATEN® Vascular Graft (6mm x 40cm, straight, standard wall, non-stretch, non-tapered)
- Bard® Impra® Vascular Graft (6mm x 40cm, straight, standard wall, non-stretch, non-tapered)

Both of these ePTFE grafts are approved for use in the US and are CE marked (i.e., are approved for use) in Europe and Israel. It is expected that the data will be pooled and that there will be no marked differences in performance between the selected ePTFE grafts (Allemang 2014, Zea 2016).

2.4.3 Rationale for Efficacy Endpoints

2.4.3.1 Patency as the Endpoint of Interest

Efficacy in the setting of vascular access in hemodialysis patients is usually focused on the usability of the conduit (patency), and on the interventions needed to maintain patency over time. Patency may be primary or secondary (Sidawy 2002). Primary Patency allows no interventions; Secondary Patency allows multiple interventions. To fully understand the utility of the HAV relative to commonly used commercially available ePTFE grafts, it is important to assess both Primary and Secondary Patency as well as the number and types of interventions used to maintain patency.

In this clinical setting, efficacy is usually analyzed by a comparison of survival curves (Kaplan-Meier Plots) – time to loss of patency, with, typically, presentation of the percent patency at fixed timepoints (usually at 6, 12, 18 and 24 months after implantation) (Dixon 2009, Huber 2003, Dember 2008, Shemesh 2015).

The biological evolution of the HAV as it is populated with cells from the subject is critical to understanding the potential advantages of the HAV, such as fewer access-related infections and longer sustained patency. However, because this evolution takes time, it is likely that early events (i.e., early thrombosis) will not be modulated significantly by the host cells that migrate into the HAV. Instead, the inherent biological properties of the HAV are more likely to translate into longer term patency – best described by Secondary Patency, which is very influenced by development of intimal hyperplasia. Furthermore, Secondary Patency (i.e., a lack of

abandonment) is a better measure of the need for a replacement conduit and protection from unnecessary utilization of anatomical sites for potential future access placement. Access placement should always start as distally as possible, ideally at the wrist and then move more proximally. Once a particular location has been used and failed it is virtually impossible to place an access more distally since the outflow vein will almost always have been compromised. Thus, in patients who have already had one or more accesses in the upper limbs the available sites become limited. It is therefore worth maintaining an existing access as long as possible - even if this requires multiple interventions – rather than to abandon that access site and move on to a new site (National Kidney Foundation 2006).

2.4.3.2 Drivers of Graft Failure

The natural history of an implanted dialysis graft is not well described; it is likely that the causes of graft failure vary over the time from graft placement – though in all cases the final failure is thrombosis:

1. Very early failures are likely related to surgical technique leading to thrombosis (e.g., twisting of the implant), immediate failure (e.g., dehiscence at an anastomosis), or thrombosis occurring because of inherent thrombogenicity of the graft material.

2. Later thromboses are most likely related to a stenosis, either within the graft itself or, more often, associated with the development of intimal hyperplasia either at the venous anastomosis, where high blood flow creates zones of high shear stress, or in the proximal vein.

3. Other factors contributing to the development of later thromboses include repeated graft punctures needed to achieve dialysis, with the associated blood flow turbulence and mechanical graft damage and pseudoaneurysms.

4. There are also non-graft related causes including post-dialysis hypotension, compression of the access following decannulation, and others usually associated with problems in the draining venous system (e.g., stenosis).

5. Other factors that may cause graft failure are infections and inappropriate dilatation.

Support for these differential drivers of thrombosis comes from a recently published study that compared the patency of standard PTFE grafts with Propaten grafts (heparin bonded) (Shemesh 2015). In that study, time to first thrombosis (loss of Primary Patency) was superior for Propaten early (up to 6 months), but not later (12 months) suggesting that the bonded heparin was able to reduce early thromboses that were likely unrelated to the inherent properties of the graft material, but that heparin did not offer benefit when thromboses were more likely to be related to stenoses (intimal hyperplasia). However, in two recent retrospective studies comparing non-heparin bound ePTFE grafts to heparin bound ePTFE grafts, neither

Allemang, nor Zea revealed improvement in patency with heparin bound grafts in the dialysis access clinical setting (Allemang 2014, Zea 2016).

2.4.3.3 Impact of the Biology of the Human Acellular Vessel on Patency

The HAV is a unique biological product - it is not a synthetic graft; it has inherent biological properties that Humacyte believes may significantly differentiate it from synthetic grafts. Furthermore, Humacyte believes that those differences are more likely to manifest themselves in the longer term, when remodeling has progressed and host cells have populated the matrix. It is of interest that in a single anecdotal case, there is evidence of 'healing' of cannulation tracts with host cell infiltration into cannulation sites.

The HAV is cultured from adult human aortic vascular smooth muscle cells, in a bioreactor that imparts arterial-like strain conditions on the growing cells. After an 8-week culture period, the tissue is decellularized, to produce the final HAV. The HAV is comprised of the ECM proteins that are secreted by the vascular smooth muscle cells during culture. These proteins include collagen types I and III, but also the glycoproteins and proteoglycans that are typically found in normal human arteries.

When host cells populate the HAV after implantation, they encounter these vascular ECM proteins. It is possible that the responses of these populating cells in the HAV may be different from the responses of host cells that infiltrate PTFE grafts. Pre-clinical work in primates (Dahl 2011) and in pigs (Quint 2011) showed that the propensity for intimal hyperplasia in decellularized HAVs was less than is typically seen in vein and PTFE grafts in pigs and baboons, respectively.

These pre-clinical studies point to a potential for the HAV to develop less intimal hyperplasia than synthetic vascular grafts. This is an important consideration since intimal hyperplasia is a common cause of graft failure and abandonment. Early data from the ongoing Phase 2 trials support the potential for longer conduit survival. The observed Secondary Patency with HAV appears to be superior to that seen in historical trials with PTFE grafts; 89% at 1 year vs 50% to 60% for synthetic grafts.

2.4.3.4 Choice of Secondary Patency as the Primary Endpoint

For the reasons described above, the study's analysis strategy is designed to examine those aspects of efficacy that primarily would be driven by the inherent biological aspects of the HAV. For these reasons, the primary objective of the study is the comparison between treatment groups of Secondary Patency, with Primary Patency as a key secondary objective.

A further consideration for selecting Secondary Patency as the primary efficacy endpoint (compared with the often use of Primary Patency) is that this is a randomized and controlled study. In this setting, the impact of physician decisions on interventions will be balanced across the two arms (not the case in historical studies which were typically single-arm assessments of

conduit performance). The prospective development by the Clinical Events Committee of clinical guidelines on management decisions will encourage physician balanced decisions about interventions to maintain patency across the two arms of the study (see 2.4.3.5 below).

2.4.3.5 Controlling against Bias

This is an open-label, comparative study. It is not possible to blind the investigators or study subjects. Study endpoints (see Section 4.2) will be determined by the clinical decisions of the investigators (except as noted below for study conduit revisions and access-related infections). To reduce the potential for bias the Clinical Events Committee (CEC) (as described in Section 9.6.2) will:

- Prospectively provide to study sites a set of clinical guidelines for study conduit interventions and abandonment.
- Review study conduit interventions and abandonment in a blinded fashion to assess compliance with these guidelines.
    - Assessments by the CEC of the appropriateness of interventions will be provided to the DMC by the CEC Coordinator (an employee of the CRO with no other study-related responsibilities). 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.
- 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, across-study 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.

2.5 Potential Risks and Benefits

2.5.1 Potential Risks

It is anticipated that subjects participating in the study will be exposed to the same risks as those associated with AV graft implantation (some of which have been reported in Phase 2 trial with the HAV – see Investigator Brochure). Risks associated with the HAV and the ePTFE graft may include, but are not limited to, the following:

- Aneurysm or pseudo-aneurysm formation
- Conduit rupture
- Bleeding and hematoma formation at the surgical site or the dialysis puncture sites
- Thrombosis/occlusion of the conduit or host vessels
- Stenosis of the conduit or its anastomoses
- Infection of the conduit, at the surgical site or a systemic infection
- Skin erosion
- Steal syndrome and/or high output cardiac failure
- Swelling of the limb

The risks anticipated in this study are similar to those associated with currently marketed prosthetic grafts used for dialysis access. There was one aneurysmal dilatation of the HAV reported in the Phase 2 experience. The superficial site of implantation of the conduit facilitates clinical and regular ultrasound monitoring, allowing any such complication to be recognized and treated promptly, and thus minimizing potential risk to the subject.

The HAV is grown using donor human aortic smooth muscle cells. The HAV is decellularized during manufacturing and thus consists of only human ECM proteins. It is possible that the HAV may provoke an immune response which may lead to damage of the HAV and possible cross reactivity against host proteins. Antibody formation will be assessed by monitoring of PRA levels.

2.5.2 Potential Benefits

Subjects who undergo implantation of the Humacyte HAV may benefit from reduced infections and improved patency, which may translate into a reduced number of interventions versus a conventional ePTFE graft. Based on the known biology of the HAV, the HAV has the potential to offer a reduced risk of infection and less intimal hyperplasia, which could offer a longer period of use (i.e., delayed abandonment).

3. STUDY OBJECTIVES

3.1 Primary Objective

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

3.2 Secondary Objectives

3.2.1 Key Secondary Objectives:

Efficacy

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

Safety

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

3.2.2 Other Secondary Objectives:

Efficacy

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

Safety

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

4. STUDY DESIGN

4.1 Description of the Study Design

This is a Phase 3, prospective, multicenter, multinational, open-label, randomized, two-arm, comparative study. Subjects who sign informed consent would undergo study-specific screening assessments within 35 days from the day of informed consent.

On the day of surgery (Day 0), subjects could still be undergoing screening assessments, such as confirmation of inclusion/exclusion criteria, to determine their eligibility before they are randomized in the study. Eligible study subjects will be randomized to receive either a HAV or one of two commercially available ePTFE grafts and followed to 24 months post-implantation at routine study visits regardless of patency status. After 24 months, subjects with a patent study conduit will be followed (while the study conduit remains patent) for up to 5 years (60 months) post-implantation at routine study visits.

4.2 Study Endpoints

4.2.1 Primary Endpoint

Time to loss of Secondary Patency from implantation

- Defined as 'the interval from the time of access placement until access abandonment', i.e., patent with or without interventions (Sidawy 2002).
- "Abandonment" defined as no remaining segment of the study conduit is 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).

4.2.2 Secondary Endpoints

4.2.2.1 Key Secondary Endpoints:

Efficacy

Time to loss of Primary Patency from implantation

- Defined as 'the interval from the time of access placement until any intervention designed to maintain or reestablish patency, access thrombosis or the measurement of patency', i.e., patent without interventions (Sidawy 2002).

Safety

Access-related infections (CDC 2013)

4.2.2.2 Other Secondary Endpoints:

Efficacy

1. Rate of interventions required to achieve/maintain Secondary Patency
2. Time to loss of Primary Assisted Patency from implantation
    a. 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).
3. Histopathological remodeling of any study conduit (based on any samples collected).
4. The efficiency of dialysis as assessed by spKt/V_{urea} (obtained from dialysis unit for a subset of subjects).

Safety

1. Frequency and severity of AEs
2. Study conduit dilatation:
    a. True aneurysm formation (conduit lumen diameter > 9 mm)
    b. Pseudo-aneurysm formation
3. Study conduit spontaneous rupture
4. Anastomotic bleeding or spontaneous rupture

4.2.3 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 >9 mm) 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

4.3 Duration of Study Participation

Each subject will be followed at study specific visits until he/she has completed 24 months of follow-up after implantation (irrespective of patency status). After 24 months, subjects with a patent study conduit will be followed (while the study conduit remains patent) for up to 5 years (60 months) post-implantation at routine study visits.

The expected duration of the clinical investigation is 76 months (initiation of enrollment through completion of data collection).

5. STUDY POPULATION

5.1 Description of the Study Population

The study population will consist of subjects with ESRD who require hemodialysis and are targeted for implantation of an AV graft for dialysis access.

5.1.1 Inclusion Criteria

1. Subjects with ESRD who are not, or who are no longer candidates for creation of an autologous AV fistula and therefore need placement of an AV graft in the arm (upper- or forearm) to start or maintain hemodialysis therapy.
2. Either on hemodialysis or expected to start hemodialysis within 12 weeks of study conduit implantation.
3. At least 18 years of age at Screening.
4. Suitable anatomy for implantation of straight or looped conduits in either the forearm or upper arm (not crossing the elbow).
5. Hemoglobin ≥8 g/dL and platelet count ≥100,000 cells/mm^3 prior to Day 0 (within 35 days).
6. Other hematological and biochemical parameters within a range consistent with ESRD prior to Day 0 (within 35 days).
7. Adequate liver function prior to Day 0 (within 35 days), defined as both of the following:
    a. ≤2x upper limit of normal (ULN) for serum bilirubin, aspartate transaminase (AST), and alanine transaminase (ALT)
    b. ≤1.5 for International Normalized Ratio (INR) or prothrombin time (PT) ≤ 18 seconds unless the subject is taking an anticoagulant at the time
8. Female subjects must be either:
    a. Of non-childbearing potential, which is defined as post-menopausal (at least 1 year without menses prior to Screening) or documented surgically sterile or post hysterectomy (at least 1 month prior to Screening)
    b. Or, of childbearing potential, in which case:
        i. Must have a negative serum or urine pregnancy test at Screening, and
        ii. Must agree to use at least one form of the following birth control methods for the duration of the study:
            1. Established use of oral, injectable or implanted hormonal methods of contraception

2. Placement of an intrauterine device or intrauterine system
3. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

9. Subject, or legal representative, able to communicate effectively with investigative staff, competent and willing to give written informed consent, and able to comply with entire study procedures including all scheduled follow-up visits.
10. Life expectancy of at least 1 year.

5.1.2 Exclusion Criteria

1. History or evidence of severe peripheral vascular disease in the intended arm for implantation.
2. Known or suspected central vein stenosis or conduit occlusion on the ipsilateral side of the planned implantation, unless the stenosis is corrected prior to study conduit implantation.
3. Treatment with any investigational drug or device within 60 days prior to study entry (Day 0) or ongoing participation in a clinical trial of an investigational product.
4. Cancer that is actively being treated with a cytotoxic agent.
5. Documented hyper-coagulable state.
6. Bleeding diathesis.
7. Active clinically significant immune-mediated disease, not controlled by maintenance immunosuppression.
    a. Low dose glucocorticoid therapy (e.g. up to 10mg a day prednisone or prednisolone) is acceptable.
    b. High dose glucocorticoid therapy for treatment of autoimmune flare, or other inflammatory diseases is excluded.
    c. Patients using glucocorticoids for immunosuppression post-transplant to prevent against transplanted allograft rejection in the period post allograft failure are excluded.
    d. The following examples of immunosuppressive agents (or the like) are exclusionary for enrollment in this clinical trial:
        i. tacrolimus or FK506 [Prograf]
        ii. mycophenolate mofetil [Cellcept],
        iii. cyclosporine [Sandimmune or Gengraf]
        iv. Sirolimus administered systemically (Sirolimus in drug eluting stents is NOT an exclusion)
8. Anticipated renal transplant within 6 months.

9. Venous outflow from study conduit cannot be placed more centrally than the venous outflow of any previous failed access on that extremity.
10. Active local or systemic infection (white blood cells [WBC] > 15,000 cells/mm^3 at Screening). If the infection resolves, the subject must be at least one week post resolution of that infection before implantation.
11. Known serious allergy to planned antiplatelet agent.
12. Pregnant women, or women intending to become pregnant during the course of the trial.
13. Any other condition which in the judgment of the investigator would preclude adequate evaluation of the safety and efficacy of the study conduit.
14. Previous enrollment in this study or any other study with HAV.
15. Employees of Humacyte and employees or relatives of the investigator.

5.2 Randomization

After a subject completes the Screening assessments, the Principal Investigator will review the subject's inclusion/exclusion criteria to determine the subject's eligibility. The Screening pages of the electronic case report form (eCRF) for eligible subjects will then be reviewed and eligibility confirmed by the Medical Monitor prior to randomization.

Study site personnel will randomize the subject 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 assigned on a 1:1 basis to the HAV or ePTFE arms of the study. The randomization will be stratified by the upper arm or forearm placement based on the Investigator's determination of where the study conduit should be located.

6. INVESTIGATIONAL MEDICINAL PRODUCT

Additional information on the manufacturing process and testing of HAV is provided in the Investigator Brochure.

6.1 Human Acellular Vessel

6.1.1 Product Description

The IMP is Humacyte's human acellular vessel (HAV), which is a tissue-engineered vascular conduit for hemodialysis access in patients with ESRD. It is a sterile, non-pyrogenic acellular tubular conduit composed of human collagen types I and III plus other ECM proteins, including fibronectin and vitronectin. The HAV is 6 mm in diameter and approximately 42 cm in length. The product is supplied on a silicone mandrel immersed in sterile, phosphate buffered saline in a sealed and labeled plastic container.

6.1.2 Manufacturer of the Investigational Medicinal Product

The HAV is manufactured by:

AlloSource
6278 S. Troy Circle
Centennial, CO 80111 USA

Traceability of the HAV during and after the clinical investigation will be achieved by the assignment of lot numbers. A unique identifying lot number will be assigned to each vessel.

6.1.3 Packaging, Storage, and Labeling

Packaging: Each HAV is contained in a sealed, flexible plastic primary container closure system that was developed by Humacyte. The system meets container/closure requirements to maintain sterility as well as product and fluid integrity. The vessel is contained inside the system in a fixed manner, immersed in a sterile, phosphate buffered saline. The total volume of the storage solution is approximately 300 mL.

Storage: The product is shipped under controlled conditions to maintain temperature at 4˚C (range: 2 – 10˚C). The product should be stored in a refrigerator that maintains this temperature range. The HAV MUST NOT be allowed to freeze.

Labeling: The IMP will be labeled according to applicable guidelines and relevant regulatory agency requirements. A tamper resistant label affixed to the secondary container will be used to ensure that the product is not compromised prior to use.

6.1.4 Implantation of the Humacyte Human Acellular Vessel

The Humacyte HAV is implanted using standard vascular surgical techniques similar to placement of synthetic or biologic AV grafts (see study manual for details).

The HAV must be delivered through the subcutaneous tissue by means of a sheath tunneler. During tunneling, the HAV should be passed through the tunneler sheath with the silicone mandrel in place to facilitate ease of delivery (see study manual for details).

6.2 Comparator Grafts

6.2.1 Product Description

The comparator in this study is one of the following commercially available 6 mm ePTFE grafts:

- Gore® PROPATEN® Vascular Graft (6mm x 40cm, straight, standard wall, non-stretch, non-tapered)
- Bard® Impra® Vascular Graft (6mm x 40cm, straight, standard wall, non-stretch, non-tapered)

6.2.2 Manufacturer of Comparator Grafts

The comparator grafts are manufactured by:

- W.L. Gore & Associates, Inc.
  Flagstaff, AZ 86004 USA
- Bard Peripheral Vascular, Inc.
  Tempe, AZ 85281 USA

Traceability of the comparator grafts during and after the clinical investigation will be achieved by tracking lot numbers for each graft.

6.2.3 Storage

The storage of the comparator grafts should follow the approved Product Information for the respective products.

6.2.4 Implantation of the Comparator Grafts

Implantation of the comparator grafts will follow standard vascular surgical techniques described in the approved Instructions for Use for the respective products.

6.3 Investigational Medicinal Product Accountability Procedures

6.3.1 Human Acellular Vessel

HAVs will be provided by Humacyte. Documentation of receipt, dispensing, and return of the HAVs must be maintained by the Principal Investigator or his/her designee. It is the Principal Investigator's responsibility to ensure that the HAVs are kept in a secure location, with access limited to individuals authorized by the Principal Investigator. The HAVs will be shipped by Humacyte or a designated representative with the IMP Receipt Form. Once signed, the IMP Form should be returned to Humacyte, and the original will be maintained in the Investigator's Files. The HAV Accountability Log will be used to account for all HAVs received, dispensed, and returned and must be maintained by the site until the conclusion of the study, at which time the original will be retrieved by Humacyte or its authorized designee and a copy kept at the site. Following final accountability of the HAVs by Humacyte or its authorized designee, all unused HAVs will be returned to Humacyte or destroyed according to procedures agreed upon with Humacyte.

6.3.2 Comparator Grafts

The comparator grafts will be provided by the study sites through commercially available stock, or by Humacyte via a third party distributor. The lot numbers for each graft used during the study will be documented.

7. OTHER TREATMENTS AND MEDICATIONS

7.1 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). 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 (as defined in Section 8).

Drugs used during anesthesia should be recorded in the anesthesia records but should not be transcribed in the eCRF.

Subjects should be questioned at each study visit concerning any new medications or changes in current medications (does not include IV fluids).

For antibiotics, the following information will be recorded in the eCRF:

- Medication generic name / components of combination product
- Dose
- Route of administration
- Frequency of administration
- Date started
- Date stopped
- Indication for use

For all other medications taken during the study, only medication name, indication for use and start and stop dates will be recorded in the eCRF.

7.2 Essential and Restricted Medications

7.2.1 Essential Medications

All subjects should receive both antibiotic and antithrombotic therapy in conjunction with HAV and ePTFE graft implantation:

Antibiotic prophylaxis:

All subjects must have at least 1 dose of antibiotic prophylaxis in accordance with local institutional guidelines. Longer antibiotic prophylaxis is at the discretion of the Principal Investigator.

Antithrombotic prophylaxis:

Intra-operative heparin: Use, dose, and route of administration of heparin during surgery are at the discretion of the investigator.

Each subject will be required to take daily aspirin (75 to 325 mg) unless he/she is already taking another antiplatelet agent. Aspirin should be initiated no later than the day after surgical implantation of the study conduit (Day 1). If low molecular weight heparin (LMWH) is administered post-operatively, aspirin or other antiplatelet agent should be initiated after stopping LMWH.

Aspirin is the recommended agent to be used for antiplatelet therapy and generally should not be combined with a second antiplatelet agent unless there is a specific indication for dual antiplatelet therapy (such as a drug eluting stent). Subjects who are known to be aspirin-sensitive should take another antiplatelet agent at the discretion of the investigator.

Anticoagulation is contraindicated unless there is a specific indication, such as deep vein thrombosis, pulmonary embolism, or atrial fibrillation. Patients already on anticoagulation at the time of screening for an appropriate medical indication can be enrolled in to the study, provided their screening data (INR, PT) at the time of medical director review indicates that it is being appropriately managed. Such patients do not require antiplatelet therapy with aspirin. Anticoagulation should be interrupted during a short perioperative window (as determined by standard of care for the site depending upon the indication for anticoagulation) and then resumed as soon as it is appropriate. If anticoagulation therapy ceases during the study the patient should start antiplatelet therapy (preferably with aspirin) as soon as possible.

7.2.2 Restricted Medications

Direct thrombin inhibitors, Factor Xa inhibitors, and vitamin K antagonists should only be given if there is a specific indication for their use.

8. STUDY PROCEDURES / EVALUATIONS

8.1 Screening (Baseline) (Day -35 to Day 0)

The screening period time window is currently specified as a maximum of 35 days from the day of consent until the day of surgery. In certain cases, the originally scheduled day of study surgery may need to be delayed due to purely logistical reasons and the subject's screening assessments may no longer fall within the current protocol-specified screening period time window. If there has been no significant change in the medical condition of the subject, it should not be necessary to repeat screening assessments or to reconsent the subject prior to study surgery. However, any extension of the screening period time window specified in the protocol, even though only for logistical reasons, must be discussed with and approved by the medical monitor prior to the day of study surgery. Subjects who have had significant medical events since screening and are now outside of the original screening window will need to be rescreened. Any relevant clinical data collected as part of standard of care since the initial screening that is within the allowed window for surgery may be used for rescreening purposes.

8.1.1 Informed Consent

The subject's informed consent must be obtained prior to any study-related procedures/activities, using the site's Institutional Review Board (IRB) / Independent Ethics Committee (IEC) approved consent form. The informed consent will cover:

- Agreement to participate in the trial for the full 5 years;
- Willingness to have study-specific medical information collected if the subject desires to stop coming for study visits. It should be noted that consent for this information collection is not a requirement for participation in the study;
- Willingness to have discarded parts of the implanted study conduit collected for histology. It should be noted that consent for collection of histology is not a requirement for participation in the study.

8.1.2 Demographics

The subject's age, gender, race and ethnicity will be recorded.

8.1.3 Medical History

A detailed medical history for each subject, including cause(s) of renal failure, history of dialysis and past vascular access procedures and smoking history will be obtained during Screening. All relevant past and present conditions that have occurred in the last 5 years will be recorded, as well as prior surgical procedures (including renal transplant history, if applicable).

8.1.4 Prior and Concomitant Medications

Record all prescription medications and aspirin that the subject is taking or has taken within 7 days prior to surgery in the subject's medical record and eCRF (see Section 7.1).

8.1.5 Physical Exam, Vital Signs and Temperature

A complete physical exam (PE) will be performed during Screening (including height and weight). The investigator or qualified medical personnel who routinely perform these evaluations in this patient population will conduct the examination, determine findings, and assess any abnormalities with respect to clinical significance. The subject's sitting blood pressure, resting heart rate and temperature will also be obtained. The patient should be carefully examined for signs or symptoms of central vein pathology as well as assessment of adequate arterial inflow.

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.

8.1.6 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed during Screening. A standard of care 12-lead ECG completed prior to consent may be used for determination of eligibility provided it occurred within the screening period time window.

8.1.7 Laboratory Evaluations

During Screening blood will be collected for the following:

- Hematology: hemoglobin, hematocrit, red blood cell (RBC), WBC with differential, platelet count.
- Clinical chemistry: sodium, potassium, calcium, blood urea nitrogen (BUN) or urea, creatinine, albumin, total bilirubin, ALT, AST, alkaline phosphatase, glucose (non-fasting).
- INR or PT (if INR value is not available)
- PRA

Additionally, either a urine sample will be obtained for women of childbearing potential to perform a urine pregnancy dipstick test or a serum pregnancy test will be performed.

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.

8.1.8 Vessel Mapping

Vessel mapping will be performed during Screening to determine whether the vessels in the operative limb are suitable for conduit implantation. Vessel mapping performed by ultrasound in the clinic by the investigator is acceptable. 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.

8.1.9 Document Reason for Not Creating a Fistula

The Principal Investigator will document the reasons why an AV graft will be implanted rather than an AV fistula created.

8.1.10 Assessment of Central Vein Stenosis

The absence of central vein stenosis will be determined by clinical criteria. If central vein stenosis or occlusion on the side in which implantation of the study conduit is planned is identified / suspected, it must be corrected before randomization.

8.1.11 Review of Eligibility for Randomization

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 randomization.

8.1.12 Serious Adverse Events

Only serious adverse events (SAEs) associated with screening procedures will be collected during the Screening period beginning from the time the subject signs the informed consent form. See Section 9 for information regarding AE/SAE collection and data handling.

8.2 Randomization and Surgical Placement of the HAV or the ePTFE Graft (Day 0)

8.2.1 Medical History and Concomitant Medications

The subject's medical history and concomitant medications (prescription medications and aspirin use) will be updated (if changed) prior to surgery. Drugs used during anesthesia should be recorded in the anesthesia records but should not be transcribed in the eCRF.

8.2.2 Symptom-directed Physical Examination, including Temperature

Perform a symptom-directed PE (if needed) and document in eCRF subject's temperature (at all visits irrespective of symptoms). The investigator or qualified medical personnel who routinely

perform these evaluations in this patient population will conduct the examination, determine findings, and assess any abnormalities with respect to clinical significance.

8.2.3 Confirmation of Eligibility and Randomization

After a subject completes the Screening assessments, the Principal Investigator will review the subject's inclusion/exclusion criteria to determine the subject's eligibility. The Screening pages of the eCRF for eligible subjects will then be reviewed and eligibility confirmed by the Medical Monitor prior to randomization.

Study site personnel will randomize the subject 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 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 equally assigned on a 1:1 basis to the HAV or ePTFE arms of the study. The randomization will be stratified by upper arm or forearm placement based on the Principal Investigator's determination of where the study conduit should be located.

8.2.4 Surgical Placement

Document the surgical procedure for implantation, including the location of the study conduit, and any complications immediately postoperatively. Indicate whether subject remained in the hospital the night after surgery; if so, indicate whether the overnight stay was planned and whether it was related to the surgery or some other reason.

8.2.5 Confirmation of Patency

Patency of, and adequate flow in, the study conduit will be confirmed intraoperatively or immediately post-surgery by the investigator's preferred method (eg. Physical exam, Doppler, ultrasound, etc) (to be documented).

8.2.6 Adverse Events

All adverse events (AEs) will be collected beginning on Day 0 after implantation up to 2 years post-implantation (Month 24). The subject will be asked general questions about his/her health and for any conduit or dialysis problems since the previous visit. See Section 9 for information regarding AE collection and data handling.

8.3 Postoperative Evaluation-Day 7-15 Visit

The initial required postoperative visit will occur anytime from Day 7 to Day 15 and will include the following assessments:

8.3.1 Concomitant Medications

Record all concomitant prescription medications and aspirin use in the eCRF.

8.3.2 Symptom-directed Physical Examination, including Temperature

Perform a symptom-directed PE (if needed) and obtain subject's temperature. The investigator or qualified medical personnel who routinely perform these evaluations in this patient population will conduct the examination, determine findings, and assess any abnormalities with respect to clinical significance.

8.3.3 Assessment of Surgical Site Healing

A clinical examination of the surgical site should be conducted and the findings documented in the eCRF.

8.3.4 Clinical Examination of Study Conduit

A clinical examination of the access site and study conduit will be performed at all postoperative study visits.

8.3.5 Document any Problems with the Access Site and Study Conduit and Interventions

Document any problems and interventions with the access site and study conduit including infections and the occurrence of thrombosis. Any procedures performed or treatments, including reasons for the procedures and dates of hospitalization, will be documented in the eCRF.

8.3.6 Assessment of Study Conduit Patency and Flow

The patency of the study conduit and adequacy of flow will be assessed by the investigator using the investigator's preferred method (eg. palpation, stethoscope auscultation, Doppler, ultrasound, etc).

8.3.7 Document Hemodialysis and Placement and/or Removal of Central Venous Catheter

Document if the subject underwent hemodialysis since the last study visit, including frequency. Document if the subject has a CVC in place or if the subject had a CVC in place since the last visit. Of particular interest is whether an alternate route for dialysis (CVC, peritoneal) is used and for how long.

8.3.8 Assessment of Adverse Events

The subject will be asked general questions about his/her health and for any conduit or dialysis problems since the previous visit. See Section 9 for information regarding AE collection and data handling.

8.3.9 Assessment of Events of Special Interest

Events of Special Interest are defined in Section 4.2.3, and the subject should be assessed at each postoperative study visit for these events. For each of these events detailed surgical notes (with illustrative diagram), including reason for and outcome of any intervention or abandonment, should be entered into the eCRF expeditiously (within 48 hours). If the event meets the criteria for a SAE (as defined in Section 9.1.1), whether or not causally related to the IMP, the event must be reported by the investigator to CTI Safety immediately (**no later than 24 hours after learning of its occurrence**).

Detailed information about the occurrence and treatment/intervention for these events will be collected throughout the study up to 5 years post-implantation. This information will include:

- Summarized surgical notes, including a simplified anatomical diagram showing where angioplasties or revisions have been made (provided intervention worksheet)
- Need for hospitalization (number of nights)
- Need for antibiotics (in the case of access-related infections)

Note: If all or part of the HAV/ePTFE is resected it should, whenever possible, be retained for future histological examination (if the subject provided his/her consent).

8.4 Postoperative Evaluation-Day 28 (±7D) Visit

8.4.1 Concomitant Medications

Record all concomitant prescription medications and aspirin use in the eCRF.

8.4.2 Symptom-directed Physical Examination, including Temperature

Perform a symptom-directed PE (if needed) and obtain subject's temperature (at all visits irrespective of symptoms). The investigator or qualified medical personnel who routinely perform these evaluations in this patient population will conduct the examination, determine findings, and assess any abnormalities with respect to clinical significance.

8.4.3 Assessment of Surgical Site Healing

A clinical examination of the surgical site should be conducted and the findings documented in the eCRF.

8.4.4 Clinical Examination of the Access Site and Study Conduit

A clinical examination of the access site and study conduit will be performed at all postoperative study visits.

8.4.5 Document any Problems with Access Site and Study Conduit and Interventions

Document any problems and interventions with the access site and study conduit including infections and the occurrence of thrombosis. Any procedures performed or treatments, including reasons for the procedures and dates of hospitalization, will be documented in the eCRF.

8.4.6 Assessment of Study Conduit Patency

The patency of the study conduit and adequacy of flow will be assessed by the investigator using the investigator's preferred method (eg. palpation, stethoscope auscultation, Doppler, ultrasound, etc).

8.4.7 Duplex Ultrasound

A duplex ultrasound will be performed to assess study conduit patency, diameter of the lumen mid-conduit, implant and anastomotic stenosis, volumetric flow rate, and to monitor for aneurysm development. The full length of the study conduit should be visualized with particular attention paid to any increase in diameter of the conduit that might indicate aneurysm formation. The methodology will be described in the study manual.

8.4.8 Determination that the Study Conduit may be used for Dialysis

Beginning on Day 28 post-implantation (±7 days), the surgeon should evaluate the study conduit to determine if it is suitable to be used for dialysis. Such suitability needs to recorded in the eCRF and transmitted to the dialysis center caring for that subject with guidance that cannulation of the study conduit for dialysis should not start before 28 days post-implantation.

If the study conduit is deemed not ready for use, either the subject should be brought back for a repeat assessment, or an intervention arranged.

8.4.9 Document Hemodialysis and Placement and/or Removal of Central Venous Catheter

Document if the subject underwent hemodialysis since the last study visit, including frequency. Document if the subject has a CVC in place or if the subject had a CVC in place since the last visit. Of particular interest is whether an alternate route for dialysis (CVC, peritoneal) is used and for how long.

8.4.10 Assessment of Adverse Events

The subject will be asked general questions about his/her health and for any conduit or dialysis problems since the previous visit. See Section 9 for information regarding AE collection and data handling.

8.4.11 Assessment of Events of Special Interest

Subjects should be assessed for the occurrence of Events of Special Interest as defined in Section 4.2.3. Detailed information about each of these events will be recorded in the eCRF as described in Section 8.3.9.

8.4.12 Laboratory Evaluations

At Day 28 (±7 days), a blood sample will be collected for the following:

- Hematology: hemoglobin, hematocrit, RBC, WBC with differential, platelet count.
- Clinical chemistry: sodium, potassium, calcium, BUN or urea, creatinine, albumin, total bilirubin, ALT, AST, alkaline phosphatase, glucose (non-fasting).

8.5 Postoperative Evaluations (Month 2 to Month 24)

8.5.1 Evaluations and Procedures to be performed at <u>All</u> Study Visits from Month 2 to Month 24

The following assessments will be performed at the Month 2 (±7D), 3 (±14D), 6 (±14D), 9 (±1M), 12 (±1M), 18 (±1M) and 24 (±1M) visits:

8.5.1.1 Concomitant Medications

All concomitant prescription medications and aspirin taken during the study up to Month 24 will be recorded in the eCRF.

8.5.1.2 Symptom-directed Physical Examination, including Temperature

Perform a symptom-directed PE (if needed) and obtain subject's temperature (at all visits irrespective of symptoms). The investigator or qualified medical personnel who routinely perform these evaluations in this patient population will conduct the examination, determine findings, and assess any abnormalities with respect to clinical significance.

8.5.1.3 Clinical Examination of the Access Site and Study Conduit

A clinical examination of the access site and study conduit will be performed at all postoperative study visits.

8.5.1.4 Assessment of Study Conduit Patency

The patency of the study conduit and adequacy of flow will be assessed by the investigator using the investigator's preferred method (eg. Physical exam [ie. palpation, stethoscope auscultation], Doppler exam, ultrasound imaging, etc).

8.5.1.5 Document any Problems with the Access Site and Study Conduit and Interventions, Including Events of Special Interest

Document any problems and interventions with the access site and study conduit including infections and the occurrence of thrombosis. Any procedures performed or treatments, including reasons for the procedures and dates of hospitalization, will be documented in the eCRF.

Subjects should be assessed for the occurrence of Events of Special Interest as defined in Section 4.2.3. Detailed information about each of these events will be recorded in the eCRF as described in Section 8.3.9. If the study conduit is abandoned, the reason for abandonment will be documented in the eCRF.

8.5.1.6 Determination that the Study Conduit may be used for Dialysis

The surgeon should evaluate the study conduit to determine if it is suitable to be used for dialysis. Such suitability needs to recorded in the eCRF and transmitted to the dialysis center caring for that subject with guidance that cannulation of the study conduit for dialysis should not start before 28 days post-implantation.

If the study conduit is deemed not ready for use, either the subject should be brought back for a repeat assessment, or an intervention arranged.

8.5.1.7 Document Hemodialysis and Placement and/or Removal of CVC

Document if the subject underwent hemodialysis since the last study visit, including frequency. Document if the subject has a CVC in place or if the subject had a CVC in place since the last visit. Of particular interest is whether an alternate route for dialysis (CVC, peritoneal) is used and for how long.

8.5.1.8 Assessment of Adverse Events

The subject will be asked general questions about his/her health and for any conduit or dialysis problems since the previous visit. See Section 9 for information regarding AE collection and data handling.

8.5.2 Evaluations and Procedures to be performed only at Specific Visits from Month 2 to Month 24

8.5.2.1 Duplex Ultrasound: Month 2, 3, 6, 12, 18 and 24

A duplex ultrasound will be performed to assess study conduit patency, diameter of the lumen mid-conduit, implant and anastomotic stenosis, volumetric flow rate, and to monitor for aneurysm development. The full length of the study conduit should be visualized with particular attention paid to any increase in diameter of the conduit that might indicate aneurysm formation.

8.5.2.2 Document Removal of CVC that was in place Pre-randomization: Month 2 and 3

Record the date and reason for removal of the CVC that was in place pre-randomization, if applicable.

8.5.2.3 Additional Data from Dialysis Unit: Month 3, 6, 12, 18 and 24

For a subset of subjects, the CRO will obtain, via data transfers from dialysis organizations, the following data obtained at a time closest but prior to the study visit (these data will be obtained from labs drawn at the discretion of the dialysis unit; where feasible and appropriate, these data will be obtained prior to study conduit implantation, too):

- spKt/V_{urea} (to enable assessment of dialysis efficiency)
- Hemoglobin
- Erythropoiesis-stimulating agent (ESA) used and dose
- HbA1c (last value prior to study conduit implantation only)

8.5.2.4 PRA: Month 6, 12, 18 and 24

PRA samples will be drawn at Month 6, 12, 18, and 24. PRA samples should also be drawn prior to transplantation for any subjects who receive a transplant during the study.

8.5.2.5 Laboratory Data: Month 6, 12, 18 and 24

At Month 6, 12, 18 and 24, a blood sample will be collected for the following:

- Hematology: hemoglobin, hematocrit, RBC, WBC with differential, platelet count.
- Clinical chemistry: sodium, potassium, calcium, BUN or urea, creatinine, albumin, total bilirubin, ALT, AST, alkaline phosphatase, glucose (non-fasting)

8.6 Month 30 to Month 60 Evaluations and Procedures

8.6.1 Evaluations and Procedures that will be performed at All Study Visits from Month 30 to Month 60 (±1M)

8.6.1.1 Symptom-directed Physical Examination, including Temperature

Perform a symptom-directed PE (if needed) and obtain subject's temperature. The investigator or qualified medical personnel who routinely perform these evaluations in this patient population will conduct the examination, determine findings, and assess any abnormalities with respect to clinical significance.

8.6.1.2 Clinical Examination of Access Site and Study Conduit

A clinical examination of the access site and study conduit will be performed at all postoperative study visits.

8.6.1.3 Assessment of Study Conduit Patency

The patency of the study conduit and adequacy of flow will be assessed by the investigator using the investigator's preferred method (eg. palpation, stethoscope auscultation, Doppler exam, ultrasound imaging, etc).

8.6.1.4 Document any Problems with the Access Site and Study Conduit and Interventions, Including Events of Special Interest

Document any problems and interventions with the access site and study conduit including infections and the occurrence of thrombosis. Any procedures performed or treatments, including reasons for the procedures and dates of hospitalization, will be documented in the eCRF.

Subjects should be assessed for the occurrence of Events of Special Interest as defined in Section 4.2.3. Detailed information about each of these events will be recorded in the eCRF as described in Section 8.3.9. If the study conduit is abandoned, the reason for abandonment will be documented in the eCRF.

8.6.1.5 Determination that the Conduit may be used for Dialysis

The surgeon should evaluate the study conduit to determine if it is suitable to be used for dialysis. Such suitability needs to recorded in the eCRF and transmitted to the dialysis center caring for that subject with guidance that cannulation of the study conduit for dialysis should not start before 28 days post-implantation.

If the study conduit is deemed not ready for use, either the subject should be brought back for a repeat assessment, or an intervention arranged.

8.6.1.6 Document Hemodialysis and Placement and/or Removal of CVC

Document if the subject underwent hemodialysis since the last study visit, including frequency. Document if the subject has a CVC in place or if the subject had a CVC in place since the last visit. Of particular interest is whether an alternate route for dialysis (CVC, peritoneal) is used and for how long.

8.6.2 Evaluations and Procedures that will be performed at Only Specific Study Visits from Month 30 to Month 60

8.6.2.1 Duplex Ultrasound: Month 36, 48 and 60

A duplex ultrasound will be performed to assess study conduit patency, diameter of the lumen mid-conduit, implant and anastomotic stenosis, volumetric flow rate , and to monitor for aneurysm development. The full length of the study conduit should be visualized with particular attention paid to any increase in diameter of the conduit that might indicate aneurysm formation.

8.7 Early Termination Visit

If a subject discontinues from the study before the Month 60 visit, then every effort should be made to perform the following early termination (ET) visit assessments. Subjects withdrawn prior to Month 24 should complete an ET visit that correlates with the procedures at Month 24. Subjects withdrawn after Month 24 and prior to Month 60 should complete an ET visit that correlates with procedures post Month 24 through Month 60.

8.7.1 Concomitant Medications (if prior to month 24)

Record any changes to the subject's prescription medications and aspirin use in eCRF.

8.7.2 Symptom-directed Physical Examination, including Temperature

Perform a symptom-directed (if needed) and obtain subject's temperature.

8.7.3 Clinical Examination of the Access Site and Study Conduit

A clinical examination of the access site and study conduit will be performed.

8.7.4 Assessment of Study Conduit Patency

The patency of the study conduit and adequacy of flow will be assessed by the investigator using the investigator's preferred method (eg. palpation, stethoscope auscultation, Doppler, ultrasound, etc).

8.7.5 Document any Problems with the Access Site and Study Conduit and Interventions, Including Events of Special Interest

Document any problems and interventions with the access site and study conduit including infections and the occurrence of thrombosis. Any procedures performed or treatments, including reasons for the procedures and dates of hospitalization, will be documented in the eCRF.

Subjects should be assessed for the occurrence of Events of Special Interest as defined in Section 4.2.3. Detailed information about each of these events will be recorded in the eCRF as described in Section 8.3.9. If the study conduit is abandoned, the reason for the abandonment will be documented in the eCRF.

8.7.6 Duplex Ultrasound

A duplex ultrasound should be performed to assess study conduit patency, diameter of the lumen mid-conduit, implant and anastomotic stenosis, volumetric flow rate , and to monitor for aneurysm development. The full length of the study conduit should be visualized with particular attention paid to any increase in diameter of the conduit that might indicate aneurysm formation.

8.7.7 Document Hemodialysis and Placement and/or Removal of Central Venous Catheter

Document if the subject underwent hemodialysis since the last study visit, including frequency. Document if the subject has a CVC in place or if the subject had a CVC in place since the last visit. Of particular interest is whether an alternate route for dialysis (CVC, peritoneal) is used and for how long.

8.7.8 Assessment of Adverse Events

The subject will be asked general questions about his/her health and for any conduit or dialysis problems since the previous visit. See Section 9 for information regarding AE collection and data handling.

8.7.9 Panel Reactive Antibodies (if prior to month 24)

Obtain a blood sample to measure PRA level.

8.8 Collection and Processing of Laboratory Samples

Blood collection will occur at the specified time points using a standard venipuncture technique. Blood collection tubes must be used in the order specified below to avoid cross-contamination of additives between tubes. The order of draw is as follows:

FIRST: Chemistry labs will be drawn first. On visits when safety labs and PRA are performed (Screening and Month 6, 12, 18 and 24), draw two tubes (no additives) – the first is for chemistry, the second is for PRA. On Day 28, draw one tube (no additives) for chemistry. [See Section 8.8.1 for processing of this sample]

SECOND: Draw one hematology tube - (EDTA tube)

Hematology and chemistry samples will be analyzed at the study site's local laboratory. PRA samples will be analyzed at a central laboratory.

8.8.1 Specimen Preparation, Handling and Shipping

Chemistry and Hematology Tubes – transport to the appropriate local clinical laboratory according to institutional procedures.

Second Non-Additive Tube for PRA testing – Allow sufficient time for the blood to clot and then centrifuge the tube to separate the serum from clotted material (if needed, based on tube used). Transfer at least 0.5 mL of serum into a pre-labeled screw cap vial (provided by Humacyte) for PRA testing. Transfer this vial to a secure, monitored freezer (≤ -20°C).

Shipment of PRA vials: Samples for PRA analysis will be shipped to Humacyte (in batches, if possible) using appropriate cooling material in an insulated container that will maintain the frozen state of the samples for the shipping period. Further details will be provided in the Study Manual.

9. SAFETY ASSESSMENTS AND ADVERSE EVENTS

The safety of the HAV and the ePTFE graft will be assessed in terms of the following:

- Anastomotic bleeding or spontaneous rupture
- Conduit dilatation (aneurysm formation [conduit lumen diameter >9 mm] or pseudo-aneurysm)
- Conduit spontaneous rupture
- Conduit infection
- Need for conduit removal
- Access-related bleeding requiring intervention
- Other AEs
- Laboratory parameters (clinical chemistry and hematology)
- Increase from baseline in PRA

9.1 Definition of 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.

It should be noted that 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.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, PE) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention

- Requires interruption or discontinuation of the IMP
- The abnormality or test result is clinically significant in the opinion of the investigator.

9.1.1 Definition of 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 (An AE is considered “life-threatening” if, in the view of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death).
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in congenital anomaly or birth defect.
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious).
- Represents a medically important event as determined by the investigator.

Medical and scientific judgment should be exercised in deciding whether AEs are serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Note: hospitalization for the surgical placement of the study conduit will not be considered an SAE. However, prolongation of the initial hospitalization due to an AE will be considered a SAE.

9.1.2 Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is any adverse drug reaction (ADR) that is serious, unexpected and suspected, meaning there is a reasonable possibility that the IMP caused the adverse event. An AE or suspected adverse reaction is considered

"unexpected" if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed.

9.2 Criteria for Determining Causal Relationship to the IMP

The criteria for determining the causal relationship of an AE with the IMP is presented in the table below.

Causal Relationship to the IMP	**Criteria for Determining Causal Relationship**
Definitely Related	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to placement of the IMP and cannot be explained by concurrent disease or other devices, drugs, or chemicals.
Possibly Related	There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after the placement of the IMP). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse effect may rate only as "possible" soon after discovery, it can be flagged as requiring more information and later be upgraded to probable or certain as appropriate.
Unlikely Related	A clinical event, including an abnormal laboratory test result, whose temporal relationship makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after placement of the IMP) and in which other drugs or chemicals or underlying disease provide plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).
Not Related	A clinical event, including an abnormal laboratory test result, which occurs when the subject was not exposed to the IMP or, another cause is obvious and in which there is sufficient information that the etiology of the event is not related to the IMP.

9.3 Criteria for Defining the Severity of an Adverse Event

Adverse events, including abnormal clinical laboratory values, will be assessed according to the criteria below and entered in the eCRF:

Grade	Severity Assessment Standard
1-Mild	Events require minimal or no treatment and do not interfere with the subject's daily activities.
2-Moderate	Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
3-Severe	Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
4-Life-threatening	Any adverse event that places the subject or participant, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.
5-Death	Death related to AE.

9.4 Reporting of Adverse Events

At each evaluation, the subject will be questioned in a general way and no specific symptoms will be suggested. If any AEs have occurred, they will be recorded on the AE pages of the eCRF and in the subject's medical record. If known, the diagnosis should be recorded in preference to the listing of individual signs and symptoms.

During the Screening period (Day -35 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 2 years post-implantation (Month 24 visit) or ET visit, whichever occurs earlier, all AEs will be reported.

During the long-term follow-up period from 2 years to 5 years post-implantation, only the following will be reported by the investigator:

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

9.4.1 Reporting of Serious Adverse Events

Any SAE which occurs during the course of this study (as defined in Section 9.1.1), whether or not causally related to the IMP, must be reported by the investigator to CTI Safety immediately (**no later than 24 hours after learning of its occurrence**).

CTI Global Safety & Pharmacovigilance

SAE Telephone Hotline: 1.877.755.0742

SAE eFax #: Country-specific fax numbers will be provided in the study manual

E-mail: CTISafety@ctifacts.com

If there are any questions, or if clarification is needed regarding the SAE, please contact the Medical Monitor in the respective region (see Section 1).

Follow-up information for the event should be sent promptly (within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records and in the eCRF.

The following minimum information is required:

- Study number,
- Subject number, gender and age,
- The date of report,
- A description of the SAE (event, seriousness of the event), and
- Causal relationship to the IMP.

Humacyte or Humacyte's designee will submit expedited safety reports to the regulatory agencies as necessary, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their IRB/IEC within timelines set by regional

regulations. Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

9.4.2 Monitoring and Reporting of Serious Adverse Events Not Related to the Implanted Conduit

Patients with ESRD have significant co-morbidities and typically experience many SAEs related to those co-morbidities that are not related to the implanted dialysis conduit. Investigators will be asked, as part of their reporting, to identify whether a particular SAE is study conduit-related.

For those events identified as not being related to the study conduit, Humacyte will monitor these events throughout the course of the study for any difference in frequency to confirm that there is not a link to the implanted conduit. Occurrences of non-conduit related SAEs will be excluded from expedited reporting to the applicable regulatory authorities and to IRB/IECs. If aggregate analysis of these events indicates they occur more frequently with the IMP, an expedited safety report may be submitted.

Regardless of whether the SAE is considered study conduit related or not, the Principal Investigator's reporting obligations for events that meet the definition of a SAE as described in Section 9.1.1 do not change.

9.4.3 Follow-Up of Adverse Events

If any AEs are present when a subject completes 2 years post-implantation or ET, if earlier, or if a subject is withdrawn from the study, the subject will be re-evaluated within an appropriate period of time. At the investigator's discretion, minor AEs can be re-evaluated via telephone and documented. If the AE has still not resolved, additional follow-up will be performed as appropriate. Every effort should be made by the investigator or delegate to contact the subject until the AE has resolved or stabilized or the medical monitor and investigator agree that further follow-up is not necessary. This should be documented in the subject's medical records.

9.5 Reporting of Pregnancy

If a study participant becomes pregnant during study participation, basic information about the pregnancy will be recorded in the Pregnancy eCRF and submitted to CTI Safety. If there are complications during the pregnancy, the complications are recorded as AEs. The participant will be asked to report the outcome of the pregnancy and the site should submit the information to CTI Safety within 30 days after the outcome of the pregnancy. If there is a congenital anomaly in the infant, this will be recorded as a SAE in the data forms for the mother (i.e., the study participant).

Partner pregnancies do not need to be reported.

9.6 Data Monitoring Committee and Clinical Events Committee

9.6.1 Data Monitoring Committee

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. 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. The DMC will consist of individuals who are not directly involved in the conduct of the study. 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.

9.6.2 Clinical Events Committee

A Clinical Events Committee (CEC) will be established to do the following:

- Prospectively provide to study sites a set of clinical guidelines for study conduit interventions and abandonment.
- Review study conduit interventions and abandonment in a blinded fashion to assess compliance with provided guidelines. Assessments by the CEC will be provided to the DMC by the CEC Coordinator (an employee of the CRO with no other study-related responsibilities).
- 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.

The CEC will consist of individuals who are not directly involved in the conduct of the study. A separate charter will be established that will describe the roles and responsibilities of the CEC.

9.7 New Information Affecting the Conduct of the Study

When new information becomes available for conducting the clinical study properly, Humacyte or designee will inform all investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

10. STATISTICAL CONSIDERATIONS

This is a prospective, multicenter, multinational, open-label, randomized, two-arm, comparative study to compare the efficacy and safety of Humacyte's HAV with that of a ePTFE graft in subjects with ESRD. The primary objective of this study is to compare the Secondary Patency of the HAV and ePTFE grafts in these subjects. The key secondary objectives of this study are to compare the Primary Patency of the HAV and ePTFE grafts, and to compare the rate of access-related infections for the HAV and ePTFE grafts.

Additional details of data handling and planned statistics are provided in the Statistical Analysis Plan.

10.1 Randomization

Subjects will be randomized 1:1 to receive an HAV or an ePTFE graft. Randomization will be stratified by arm placement location (upper arm versus forearm placement) based on the Investigator's determination of where the study conduit should be located. Randomization by country will be used to ensure there is approximately the same count of subjects in each treatment group across each country. Prior to surgery the subject's eligibility will be reviewed by the Investigator and confirmed by the Medical Monitor. During surgery the Investigator will determine the implantation site (forearm versus upper arm) and confirm that the subject is not a candidate for creation of an autologous AV fistula. Randomization may occur once the arterial and venous exposures have been completed with confirmation of adequate arterial inflow and venous outflow.

10.2 Analysis Population

Efficacy

The primary analysis will be in the Intent-to-Treat (ITT) population with confirmatory analyses in the modified Intent-to-Treat (mITT) and Per Protocol (PP) populations.

The ITT population is defined as all randomized subjects (based on study conduit group assignment).

The mITT population is defined as all subjects in whom a study conduit has been implanted (based on actual conduit implanted).

The PP population is 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.

Safety

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

10.3 Efficacy Analysis

10.3.1 Censoring for Time to Event Analyses

- Subjects who have patent study conduits at the time of death, kidney transplant or withdrawal will be censored at that timepoint (additional efficacy analyses will consider death as an event-see Section 10.3.4).

- 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 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 was made.

These censoring rules will apply to all 'time to' analyses.

10.3.2 Primary Efficacy Analysis

The primary efficacy endpoint is the time to loss of Secondary Patency.

Study endpoints (see Section 4.2) will be determined by the clinical decisions of the investigators except for the following events that will be adjudicated by the CEC:

- Study conduit revisions to determine whether the original study conduit was still being used for dialysis.

- Access-related infections using the Centers for Disease Control and Prevention (CDC) definitions for dialysis-associated infections (CDC 2013).

The outcome of these adjudications will be used as endpoints in the trial rather than the investigator determinations.

The primary analysis will be a non-inferiority analysis, which will be conducted when all subjects are at least 18 months post-implantation.

The primary analysis will be in the ITT population with confirmatory analyses in the mITT and PP populations.

The following rules will apply to the ITT population:

- Subjects in whom the wrong study conduit was 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.

The hazard ratio (HAV relative to ePTFE) will be estimated using a Cox proportional hazards regression model with treatment group and the randomization stratification variable as factors. Based on the estimated 18-month event-free rate in the ePTFE arm, the non-inferiority margin will be determined by the hazard ratio corresponding to a difference of 10 percentage points. If the lower limit of the two-sided 95% confidence interval for the hazard ratio is greater than the corresponding non-inferiority bound, then non-inferiority will be demonstrated.

10.3.3 Key Secondary Efficacy Analyses

If the primary efficacy analysis demonstrates non-inferiority, the following key secondary analyses will be completed at the same timepoint in the ITT population 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 as follows:

- Superiority analysis of the time to loss of Secondary Patency
- Non-inferiority analysis of the time to loss of Primary Patency
- Superiority analysis of the time to loss of Primary Patency

The non-inferiority analysis of time to loss of Primary Patency will be completed using the same statistical approach and non-inferiority margin as specified for the primary analysis.

The superiority analyses will be completed using the same statistical model as described for the corresponding non-inferiority analysis. The two arms will be compared using a two-sided test at the alpha=0.05 level of significance.

10.3.4 Additional Efficacy Analyses

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.

In the primary and key secondary analyses of Primary Patency and Secondary Patency, death will be treated as a censored outcome. These analyses will be repeated as supportive analyses with death treated as an event. Additionally, a time to event analysis will be conducted for all censored subjects and any subjects who withdraw for any reason.

The rates 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 randomization stratification variable as factors.

Secondary endpoints that are defined as time-to-event variables will be summarized using the Kaplan-Meier method and analyzed using the log-rank test. Proportion endpoints will be analyzed using Pearson's chi-square test and all other quantitative endpoints will be analyzed using the two-sample t-test.

All secondary analyses that are superiority comparisons will be carried out using two-sided tests at the alpha=0.05 level of significance, with no adjustment for multiplicity.

Any analysis of histopathological remodeling on any study conduit will be descriptive only.

10.4 Safety Analysis

The safety analysis will be conducted in the safety population.

For each of the two treatment groups, the access-related infection rate will be computed in 2 ways:

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

These analyses will be based on adjudicated events using a standardized definition of access-related infections (CDC 2013).

For each of the 2 definitions, the infection rates in the two arms will be compared using a Poisson regression model with treatment group and the randomization stratification variable as factors. This analysis will be conducted using a two-sided test at the alpha=0.05 level of significance.

All other safety data will be described only (i.e., no inferential statistics).

For the analysis of study conduit dilatation and aneurysm formation, descriptive data will be presented by Visit. In addition, the number of study conduits showing true aneurysm formation (internal conduit diameter >9 mm) or pseudo-aneurysm will be reported.

10.5 Sample Size

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 arm 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:

- 90% power to demonstrate non-inferiority (non-inferiority margin=10%) 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 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. 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.

11. STUDY MANAGEMENT AND DATA COLLECTION

11.1 Ethical Conduct of the Trial

This study will be conducted according to the protocol; applicable national regulations; the World Medical Association Declaration of Helsinki and Good Clinical Practice (GCP, International Conference on Harmonization [ICH] E6). Each investigator will conduct the trial according to applicable local or regional regulatory requirements.

11.2 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

Humacyte shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

Humacyte affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials (where allowed by local or national regulations) will identify subject data retrieved by Humacyte. However, Humacyte requires the Investigator to permit Humacyte, Humacyte's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

Humacyte will ensure that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information.

11.3 Institutional Review Board /Independent Ethics Committee

Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) must be constituted according to the applicable requirements, including ICH GCP.

It is the responsibility of each Principal Investigator (or designee such as the CRO) to submit the protocol, Investigator Brochure, subject informed consent, subject recruitment materials (if applicable), and other documentation as required by the IRB/IEC to his/her IRB/IEC for review and approval. A copy of the written approval must be provided to the CRO. The documentation should clearly mention the approval/favorable opinion of the protocol, the subject informed consent form, and subject recruitment materials (if applicable), including respective version

dates. The written approval and a list of current membership, or Department of Health and Human Services (DHHS) Assurance Number or letter from the IEC/IRB stating that the membership list is on file, must be obtained from the IRBs/IECs and provided to the CRO prior to the release of clinical study supplies to the investigational site and commencement of the study. If any member of the IRB/IEC has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained.

Each investigator must adhere to all requirements stipulated by his/her respective IRB/IEC. This includes notification to the IRB/IEC regarding protocol amendments, updates to the subject informed consent, recruitment materials intended for viewing by subjects, expedited safety reports, SAEs and unexpected AEs, reports and updates regarding the ongoing review of the trial at intervals specified by the respective IRB/IEC, and submission of final study reports and summaries to the IRB/IEC.

11.4 Subject Informed Consent

Subjects must sign and date an IRB/IEC-approved informed consent form prior to any study procedures being performed. Each subject will receive a signed and dated copy of the informed consent. In addition, this information should be recorded in the subject's medical record (i.e., source document).

The subject will be asked to sign for 3 aspects of the study: consent to participate in the study, consent to allow the study doctor to follow-up with his/her health care providers in the event the subject decides to stop attending study visits and consent to allow for study doctors to collect any samples or study conduits to be used for histology. It should be noted that the consent for collection of histology is not a requirement for participation in the study.

The written consent document will embody the elements of informed consent as described in the World Medical Association Declaration of Helsinki, applicable national regulations, ICH E6 guideline (GCP), and in accordance with any local regulations. The investigator (or designee such as the CRO) is responsible for the preparation, content, and IRB/IEC approval of the informed consent document. The consent form must be approved by the site's IRB/IEC and be acceptable to Humacyte.

The consent form must be written in a language fully comprehensible to the prospective subject. The investigator or designee shall give the subject adequate opportunity to read it before it is signed and dated. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB/IEC. Subjects must be given ample opportunity to inquire about details of the study.

11.5 Substantial Amendments to the Protocol

A substantial amendment must be agreed to in writing by Humacyte and submitted to and approved by the respective regulatory authority and IRB/IEC before the amendment can be implemented. Written approval of a protocol amendment is not required prior to implementation of changes to the protocol which eliminate an immediate hazard to the study subject; however, approval must be obtained as soon as possible thereafter. Any amendments must also be signed by the Principal Investigator.

11.6 Study Initiation

The Principal Investigator must not enroll any subjects prior to attendance at the Investigator Meeting or the completion of a formal site initiation visit conducted by the CRO. These meetings will include a detailed review of the study protocol and eCRF pages. The investigator will not be supplied with IMP until all necessary pre-study requirements have been completed and signed essential documents provided to the CRO.

11.7 Study Monitoring

It is the responsibility of the Principal Investigator to ensure that the study is conducted in accordance with the protocol, GCP, applicable regulatory requirements, and the currently approved Declaration of Helsinki, and that valid data are entered in the eCRF.

To achieve this objective, the monitor's duties are to ensure the maintenance of complete, legible, well-organized, and easily retrievable data. The monitor will review the protocol with the investigator. In addition, the monitor will explain the investigator's reporting responsibilities and all applicable regulations concerning the clinical evaluation of the IMP.

The investigator will permit representatives of Humacyte and the CRO to monitor the study as frequently as Humacyte or the CRO deem necessary to determine that data recording and protocol adherence are satisfactory. The eCRF data and related source documents will be reviewed in detail by the monitor at each visit, in accordance with relevant Standard Operating Procedures (SOPs) and ICH GCP regulations. This includes results of tests performed as a requirement for participation in this study and any other medical records required to confirm information contained in the eCRF such as past medical history and secondary diagnoses. The investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.8 Case Report Form

An eCRF will be used for this study. The data will be entered in the eCRF in a timely manner on an ongoing basis.

The Principal Investigator is responsible for ensuring that data are properly recorded in each subject's eCRF and related documents. The Principal Investigator should personally sign the eCRFs in accordance with the procedure described in the eCRF completion guidelines to ensure that the observations and findings are correct and complete.

For data handled by the CRO, eCRF data and some or all of the study-related data will be managed and stored electronically in the CRO's database system. Validated data will subsequently be transferred to Humacyte.

11.8.1 Data Management

Data management will be coordinated with Humacyte or designee in accordance with the SOPs for Data Management. All study specific processes and definitions will be documented by Data Management. eCRF completion and correction processes will be referenced in the eCRF instructions. Coding of medical terms will be performed using the Medical Dictionary for Regulatory Activities (MedDRA).

11.9 Verification Procedures

It is the investigator's obligation to ensure documentation of all relevant data in the subject's medical record. The subject's medical record will be considered the source document. The eCRF should not be used as the source for study information.

The investigator will maintain a subject identification code list to enable unambiguous identification of the subjects (subject names and corresponding subject numbers). The subject identification code list is an essential document and as such should be maintained according to the ICH GCP guidelines.

11.10 Retention of Records

All documentation pertaining to the study will be kept by Humacyte or its designee in accordance with ICH guidelines and applicable national and local regulations.

The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating subjects, medical records, study-specific source documents, source worksheets, all original signed and dated informed consent forms, query responses, and detailed records of IMP disposition to enable evaluations or audits from regulatory authorities and Humacyte or its designees. These documents are to be retained until

at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or if needed by Humacyte. Humacyte will notify the site/investigator if the marketing application is approved or if the IND/Investigational Medicinal Product Dossier (IMPD) is discontinued. The investigator agrees to obtain Humacyte's agreement prior to disposal, moving, or transferring of any study-related records. Humacyte will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records. All data will be entered into the eCRFs supplied for each subject.

11.11 Protocol Deviations

A protocol deviation is any noncompliance with the protocol or associated GCP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Although in principle protocol deviations are not permitted, under emergency circumstances, deviations may proceed without prior approval of Humacyte and the IRB/IEC to protect the rights, safety, and well-being of human subjects.

All protocol deviations will be documented and reported by the CRO during the course of the study in the monitoring reports. All deviations will be reported to Humacyte who will agree on the necessary actions to be taken.

If required per their guidelines, reports about protocol deviations must be provided to the local IRB/IEC.

11.12 Insurance and Indemnity

Insurance coverage for damages emerging from the study will be provided according to applicable legal requirements. During the informed consent procedure, the investigator must inform the subject accordingly.

11.13 Audit

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/IRB will be granted access to the site and relevant study documentation to perform audits or inspections. The Principal Investigator should contact Humacyte immediately if contacted by a regulatory agency about an inspection involving this protocol.

12. REPORTING

Following completion of follow-up of all subjects to the 12-month endpoint, a clinical study report will be generated, including a summary of all available data, statistical measures, tabulated results, graphical results and interpretations. This report will be submitted to regulatory authorities in a timely manner. Addenda to the report will be generated and submitted to regulatory authorities that will include data up to 24 months, and then up to 60 months follow-up or based on timing otherwise to be defined.

12.1 Quality Control and Quality Assurance

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and applicable regulatory requirements. Reports of monitoring activities will be submitted to Humacyte in a timely manner.

The investigational site will provide direct access to all trial related areas, source data/documents, and reports for the purpose of monitoring and auditing by Humacyte, and inspection by local and regulatory authorities.

Quality control procedures will be implemented for data entry and data quality control checks will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

13. RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR

The role of the Principal Investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as to ensure data integrity and the rights, safety, and well-being of the subjects involved in the clinical investigation.

13.1 Informed Consent

The Principal Investigator shall ensure that the process for obtaining informed consent:

- Includes all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation
- Avoids any coercion or undue improper influence on, or inducement of, the subject to participate
- Does not waive or appear to waive the subject's legal rights
- Uses native non-technical language that is understandable to the subject
- Provides ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation
- Provides the subject with a copy of the signed and dated informed consent form and any other written information

The Principal Investigator shall ensure and document appropriate training if an authorized designee is appointed to conduct the informed consent process.

13.2 Compliance with the Protocol

The Principal Investigator shall:

- Indicate his/her acceptance of the protocol in writing
- Conduct the clinical investigation in compliance with the protocol
- Create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits
- Ensure that the IMP is used solely by authorized users, and in accordance with the protocol and instructions for use

- Propose to Humacyte any appropriate modification(s) of the protocol
- Refrain from implementing any modifications to the protocol without agreement from Humacyte, IRB/IEC, and, if required, regulatory authorities
- Document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to Humacyte in the eCRFs and in all required reports
- maintain the IMP accountability records
- Allow and support Humacyte to perform monitoring and auditing activities
- Be accessible to the monitor and respond to questions during monitoring visits
- Allow and support regulatory authorities and the IRB/IEC when performing auditing activities
- Ensure that all clinical-investigation-related records are retained as specified in this protocol

13.3 Medical Care of Subjects

The Principal Investigator shall:

- Provide adequate medical care to a subject during and after a subject's participation in a clinical investigation in the case of AEs
- Inform the subject of the nature and possible cause of any AEs experienced
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required

- Provide the subject with well-defined procedures for possible emergency situations related to the clinical investigation, and make the necessary arrangements for emergency treatment

- Ensure that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical investigation

- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation

- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from the clinical investigation while fully respecting the subject's rights

13.4 Safety Reporting

The Principal Investigator shall:

- Record every AE together with an assessment, in accordance with Section 9 of this protocol

- Report to Humacyte, without unjustified delay, all SAEs and medically significant events as specified in Section 9.1.1 of this protocol

- Supply Humacyte or designee, upon Humacyte's request, with any additional information related to the safety reporting of a particular event

14. SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

Humacyte may suspend or prematurely terminate either a clinical investigation (study) at an individual investigative site or the entire clinical investigation for significant and documented reasons.

A Principal Investigator, IRB/IEC, or regulatory authority may suspend or prematurely terminate participation in a clinical investigation at the investigation sites for which they are responsible.

If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so requested by the IRB/IEC or regulatory authorities, Humacyte shall suspend the clinical investigation while the risk is assessed. Humacyte shall terminate the clinical investigation if an unacceptable risk is confirmed.

Humacyte shall consider terminating or suspending the participation of a particular investigation site or investigator if monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication.

If, for any reason, Humacyte suspends or prematurely terminates the investigation at an individual investigation site, Humacyte shall inform the responsible regulatory authority if required and ensure that the IRB/IEC is notified. If the suspension or premature termination was due to a safety-related reason, Humacyte shall inform all other principal investigators.

If suspension or premature termination occurs,

1. Humacyte shall remain responsible for providing resources to fulfill the obligations from the protocol and existing agreements for following up the subjects enrolled in the clinical investigation, and

2. the Principal Investigator or authorized designee shall promptly inform the enrolled subjects at his/her investigation site, if appropriate.

In the event that the study is discontinued, the reasons for discontinuation will be explained to the investigators and may be disclosed to the study participants. Humacyte will provide all information needed by the investigator to ensure the safety and well-being of the study participants.

15. PUBLICATION POLICY

Information concerning the IMP, patent applications, processes, unpublished scientific data, the Investigator Brochure and other pertinent information is confidential and remains the property of Humacyte. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that Humacyte will use the information obtained during the clinical study in connection with the development of the IMP and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide Humacyte with all data obtained during the study.

The study will be considered for publication or presentation at (scientific) symposia and congresses. A Publication Committee comprising a selected group of investigators, a statistician and a representative from Humacyte will oversee all publication of data from this study. Members of this committee will fulfill the criteria of the International Committee of Medical Journal Editors (ICMJE) for authorship of a scientific publication in relation to this study.

If the proposed publication/disclosure risks Humacyte's ability to patent any invention related to the study, the publication or disclosure will be modified or delayed a sufficient time to allow Humacyte to seek patent protection of the invention.

The first publication or disclosure of the results of this study will be a complete, joint multicenter publication or disclosure. Subsequent publication or presentation of data (entire or a subset) from the study will be permitted provided that the first publication is adequately referenced.

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APPENDIX 1: VISIT SCHEDULE

	Screening D -35 to D 0	**D 0**	**D 7-15[11]**	**D 28**	**M 2**	**M 3**	**M 6**	**M 9**	**M 12**	**M 18**	**M 24**	**M 30-60 at 6M intervals**	**ET[12]**
Visit Window	--	--	--	±7 D	±7 D	±14 D	±14 D	±1 M	±1 M	±1 M	±1 M	±1 M	--
Informed consent	X												
Demographics	X												
Medical history	X	X											
Concomitant medications[1]	X	X	X	X	X	X	X	X	X	X	X		X
Physical exam and temperature[2]	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
ECG (12-lead)	X												
Vessel mapping[3]	X												
Document reason for not creating a fistula	X												
Assessment of central vein stenosis	X												
Confirmation of eligibility (inclusion/exclusion criteria)[4]	X	X											
Randomization during surgery		X											
Surgical placement of study conduit and documentation of any complications		X											
Labs[5]	X			X			X		X	X	X		
PRA[6]	X						X		X	X	X		X
Assessment of surgical site healing			X	X									
Clinical examination of access site and study conduit			X	X	X	X	X	X	X	X	X	X	X
Documentation of problems with			X	X	X	X	X	X	X	X	X	X	X

access site and study conduit and interventions													
Assessment of Study Conduit Patency		X	X	X	X	X	X	X	X	X	X	X	X
Duplex Ultrasound Examination [7]				X	X	X	X		X	X	X	X	X
Determine suitability of study conduit for dialysis[8]				X	X	X	X	X	X	X	X	X	
Document removal of pre-randomization CVC (if applicable)					X	X							
Visits associated with transfer of dialysis efficiency data & additional lab data from dialysis organizations to CRO (in subset of subjects)[9] – no site action needed						X	X		X	X	X		
Document hemodialysis / CVC use			X	X	X	X	X	X	X	X	X	X	X
Adverse Events / Events of Special Interest[10]	X	X	X	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.

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 24 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 randomization.

5: Labs include hematology and chemistry. Screening labs will also include INR (or PT 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. PRA samples should be drawn prior to transplantation for any subjects who receive a transplant during the study prior to Month 24.

7: 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 study conduit. At all other timepoints (except Month 9), duplex ultrasound will be used to assess patency, diameter of the lumen mid-conduit and flow rate and to monitor aneurysm development. After Month 24, a duplex ultrasound is to be performed at Month 36, 48 and 60.

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

9: Dialysis efficiency (spKt/Vurea) and additional lab data (hemoglobin, ESA used and dose and HbA1c) will be obtained from dialysis organizations for a subset of subjects via data transfers to the CRO. These data will be obtained from labs drawn at the discretion of the dialysis unit; where feasible and appropriate, these data will be obtained prior to study conduit implantation, too (HbA1c will be obtained pre-implantation only, when possible). No site involvement is required in this process.

10: 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 24 visit. After the Month 24 visit up to Month 60, only the following will be reported by the investigator:

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

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

12: Subjects withdrawn prior to the Month 60 visit will have ET assessments performed. Subjects withdrawn prior to Month 24 should complete an ET visit that correlates with the procedures at Month 24. Subjects withdrawn after Month 24 and prior to Month 60 should complete an ET visit that correlates with procedures post Month 24 through Month 60.