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

Medicinal Product:	Human Acellular Vessel (HAV)
Study No.:	CLN-PRO-V011

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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 Polish regulatory requirements

Site Principal Investigator Agreement Page for the Protocol

Protocol Version 1.2 Dated: 18 December 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 Competent Authority, 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 Executive Officer / Chief Medical Officer, Humacyte, Inc.

Signed:  Date: 19Dec2018

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List of Abbreviations

AE	Adverse event
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
CSR	Clinical Study Report
CVC	Central venous catheter
D	Day
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECM	Extracellular Matrix
eCRF	Electronic case report form
ePTFE	Expanded polytetrafluoroethylene
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
IEC	Independent ethics committee
IgG	Immunoglobulin G
IMP	Investigational medicinal product
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional Review Board
K-M	Kaplan Meier
LMWH	Low molecular weight heparin

List of Abbreviations

M	Month
PAD	Peripheral arterial disease
PE	Physical examination
PRA	Panel reactive antibody
PT	Prothrombin time
PTFE	Polytetrafluoroethylene
RBC	Red blood cell
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
US	United States
WBC	White blood cell

Protocol Summary

Full Title	A Phase 2 Assessment of Humacyte's Human Acellular Vessel in Patients Needing Vascular Access for Dialysis
Clinical Trial Phase	Phase 2
Sponsor	Humacyte, Inc.
Planned Study Sites	2 sites in Poland
Sample Size	Up to 30 patients implanted with a Human Acellular Vessel (HAV)
Expected Enrollment Start	2Q 2019
Study Rationale	Previous studies with the HAV have used Investigational Medicinal Product (IMP) manufactured using small-scale systems (Aura and Terra). Prior to commercialisation, manufacturing has been switched to a larger-scale automated process with greater in-process controls (Luna). Based on a large number of preclinical parameters, including those used for batch release, the IMP manufactured using the Luna system is comparable to that used in earlier clinical studies. This study will allow confirmation of the short-term safety, efficacy and absence of immunogenicity of the Luna product.
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	2 months
Study Duration	Each subject will be followed by study specific visits until he/she completes 1 year (12 months) of follow-up after implantation (irrespective of patency status). After 1 year, only subjects with a patent HAV will be followed (while the HAV remains patent) for up to 3 years (36 months) post-implantation at study visits every 6 months. The expected duration of the clinical investigation is 41 months (initiation of enrollment through completion of data collection).
Study Design	Prospective, two center, open-label, single-arm study.
Intervention Description	The IMP is Humacyte's HAV, which is a tissue-engineered vascular conduit for hemodialysis access. HAVs for this study will be manufactured using the Luna commercial manufacturing system. Subjects will be implanted with an HAV in the forearm or upper arm

	using standard vascular surgical techniques. 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 HAV (Day 1). If low molecular weight heparin (LMWH) is administered post-operatively, aspirin or other antiplatelet agents 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 evaluate the safety, efficacy and immunogenicity over 3 months after implantation of HAVs manufactured using the commercial manufacturing system (Luna)
Secondary Objectives	To evaluate the long-term safety and efficacy of the HAV (manufactured with the Luna system) over a period of up to 36 months after implantation
Inclusion Criteria	1. Subjects with ESRD who are not, or who are no longer, candidates for creation of an autologous AV fistula (AVF) and who need placement of an AV graft in the arm (upper- or forearm) for hemodialysis therapy. 2. Already established on hemodialysis. 3. At least 18 years of age at Screening. 4. Suitable arterial and venous 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 45 days). 6. Other hematological and biochemical parameters within a range consistent with ESRD prior to Day 0 (within 45 days). 7. Normal clotting (international normalized ratio [INR] ≤ 1.5 or prothrombin time ≤ 18 sec unless the patient is taking an anticoagulant for an approved indication at the time of HAV implantation. 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 HAV 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 as defined as either: a. a biochemical diagnosis (e.g. Factor V Leiden, Protein C deficiency, etc.) - OR – b. a clinical history of thrombophilia as diagnosed by 2 or more spontaneous intravascular thrombotic

	events (e.g. deep vein thrombosis, pulmonary embolism, etc.) within the 5 previous years. 6. Spontaneous or unexplained bleeding diathesis clinically documented within the last 5 years or a biochemical diagnosis (e.g. von Willebrand disease, etc.). 7. Active clinically significant immune-mediated disease, not controlled by maintenance immunosuppression (low dose steroid therapy only) a. Low dose glucocorticoid therapy (e.g. up to 10 mg 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 HAV 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 1 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 HAV. 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 Endpoints – assessed at 3 months post implantation	Safety • Adverse events indicating possible mechanical failure or weakness of the HAV (anastomotic rupture, anastomotic bleeding, spontaneous HAV rupture, aneurysm, pseudoaneurysm, abnormal post cannulation hemostasis) • HAV infections • Change from baseline of panel reactive antibody (PRA) and anti-HAV IgG levels (at 2 months) • All adverse events (AEs)/serious adverse events (SAEs) and adverse events of special interest. Efficacy • Primary / primary assisted/secondary patency
Secondary Endpoints – assessed throughout the 36 month follow up	Safety • Adverse events indicating possible mechanical failure or weakness of the HAV (anastomotic rupture, anastomotic bleeding, spontaneous HAV rupture, aneurysm, pseudoaneurysm, abnormal post cannulation hemostasis) • HAV infections • Change from baseline of PRA and anti-HAV IgG values (at 12 months) • All AEs/SAEs until 12 months post implant, after that only SAEs related to the HAV and adverse events of special interest Efficacy • Primary/primary assisted/secondary patency • Interventions required to achieve/maintain secondary patency. • Histopathological remodeling of any HAV (based on any

	samples collected).
Data Analysis	This is an exploratory study with no formal hypothesis testing. Data will be summarized using descriptive statistics only. All available data will be summarized and reported in a clinical study report (CSR) when the last patient completes 3 months of follow up. A second analysis will be conducted when all patients have completed 12 months of follow up. The final analysis will occur when the final patient completes 36 months of follow up.
Study Oversight **Data Monitoring Committee (DMC)**	An independent Data Monitoring Committee (DMC) has been established to review safety on an ongoing basis across the entire clinical program and to provide recommendations about stopping, continuing or otherwise modifying studies. Responsibilities of the DMC will include review of safety data from this study. DMC will review data from this study on an ongoing basis with the 1st scheduled DMC review after the last patient completes Month 3 and every 6 months thereafter. The DMC consists of individuals who are not directly involved in the conduct of the study. A separate charter has been established that describes the roles and responsibilities of the DMC.
Protocol Approval **(Version and Date)**	v1.2 18 December 2018

1. STUDY PERSONNEL

A 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 or the CRO.

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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. 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 6 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 Scientific Rationale

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

2.2 Summary of 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 immune response. No delayed-type hypersensitivity reactions were observed in any animals.

Biocompatibility assessments of the HAV ECM were conducted in accordance with internationally-recognized (International Organization for Standardization) 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 Clinical Studies

2.3.1 Overview

The HAV clinical development program currently includes 7 clinical studies: 4 in patients with end-stage renal disease receiving hemodialysis (CLN-PRO-V001, CLN-PRO-V003, CLN-PRO-V006 and CLN-PRO-V007), 2 in patients with peripheral arterial disease (CLN-PRO-V002 and CLN-PRO-V004) and 1 in patients with vascular trauma (CLN-PRO-V005). Three Phase 1/2 studies have completed primary analysis with long-term follow-up ongoing (CLN-PRO-V001, CLN-PRO-V002 and CLN-PRO-V003), 1 phase 3 study completed enrollment and follow-up is ongoing (CLN-PRO-V006), 2 Phase 2 studies (CLN-PRO-V004, CLN-PRO-V005) and 1 phase 3 study (CLN-PRO-V007) are open for enrollment.

As of 10 April 2018, 272 patients (244 hemodialysis access patients and 28 peripheral arterial disease [PAD] patients) have received a HAV. The first implant for hemodialysis was performed in December 2012, and the first peripheral arterial bypass in October 2013. Overall, the total treatment exposure is approximately 329 patient years in the hemodialysis access population and 55 patient years in the PAD population. More information on the clinical profile of the HAV in these ongoing studies is provided in the Investigator Brochure.

2.3.2 Experience in Dialysis Patients

Two Phase 2 trials, 1 in Poland (CLN-PRO-V001) and 1 in the United States (US) (CLN-PRO-V003) have completed enrollment. Both recruited subjects requiring hemodialysis access for end-stage renal disease whom were not suitable for creation of an AVF. Most subjects had undergone previous vascular access procedures, in many cases multiple attempts including both AVFs and synthetic grafts. Initial results from these Phase 2 studies are discussed below.

The primary objectives of these 2 studies are to evaluate both the safety of HAV and its efficacy in terms of primary and secondary patency at 6 months. Secondary objectives include measurement of a PRA response, development of IgG antibodies to the extracellular matrix material in the HAV and a 2 year evaluation of patency and an assessment of the need for interventions to maintain/restore patency. Follow up has now been extended up to 120 months.

A phase 3 randomized study comparing HAV with expanded PTFE (ePTFE) grafts (CLN-PRO-V006) has completed enrollment in the US, Europe, and Israel. A second phase 3 randomized study (CLN-PRO-V007) comparing HAV with AVF is currently enrolling in the US. As the sponsor is blinded, no efficacy information currently available for the phase 3 studies; however, blinded safety data is presented in the Investigator Brochure.

2.3.2.1 CLN-PRO-V001 and CLN-PRO-V003 Study Results (24 M)

All subjects (n = 60) have now completed at least 24 months since implantation (or had a censoring event). The first subjects recruited are now beyond 60 months after HAV implantation, some with functioning HAV for hemodialysis access. Together these 2 trials provide more than 150 years of follow up during which the HAV has been used for more than 15,000 hemodialysis sessions.

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 dialysis catheter. One non-serious arteriovenous graft aneurysm was reported in Study CLN-PRO-V001 (moderate in intensity, considered possibly related to IMP and considered not related to procedure – this patient died before the Sponsor could complete the follow up of this event). An expected number of small pseudoaneurysms have been observed, which is consistent with all surgically-created hemodialysis access. Most have resolved spontaneously with only 2 cases requiring surgical intervention. Flow rates through the HAV were more than sufficient to allow for effective dialysis.

In both 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 1 or more renal transplant failures; 1 subject recently; 1 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.

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 1 case the IgG titer increase occurred in a subject who maintained primary patency.

Adverse events (AEs) related to the HAV/access site (excluding thrombotic events) were few; there have been only 3 access-site infections, of which only 1 required removal of part of the HAV. There have been:

- 1 kidney transplant (known to be functioning well at 12 months post-transplant)
- 15 deaths, all after abandonment or during follow-up; none of the deaths were considered related to the presence of the HAV

Patency data for the 2 studies in dialysis access has been pooled for a combined Kaplan-Meier (K-M) analysis (Lawson, 2016). Based on these K-M plots the patency at 6, 12 and 24 months is estimated to be 60%, 26% and 15% (primary patency) and 97%, 91% and 77% (secondary patency).

2.3.3 Experience in Peripheral Arterial Bypass Patients

Humacyte has 2 Phase 2 studies to assess the safety and efficacy of the HAV when used as an above-knee arterial bypass graft. The first study, CLN-PRO-V002, is a single group uncontrolled study conducted at 3 sites in Poland that is fully enrolled and in long-term follow up. Eligible patients required a femoro-popliteal bypass graft for the management of symptomatic peripheral arterial disease. Pre-operative imaging (conventional or computed tomography [CT] angiography) must have demonstrated at least 2 below knee vessels patent to the ankle with good runoff. The proximal anastomosis was expected to be below the inguinal ligament and the distal anastomosis above the knee. Autologous vein grafts must not have been suitable or feasible (e.g., because of severe venous disease or prior use of leg veins for other bypass surgery or there is a clinical need to preserve those veins for future bypass surgery in the coronary or peripheral circulation).

The HAV was implanted using standard vascular surgical techniques and the patency of the bypass confirmed by intraoperative angiography (conventional or intra-op CT angiography) or ultrasound. The patient was then followed up at study visits at 15 days, 6 weeks and 3, 6, 12, 18 and 24 months. At each visit safety was assessed by clinical examination and adverse events, and the HAV was examined using duplex ultrasound to visualize the entire length to confirm patency, flow and to detect stenosis, aneurysm development or dilatation.

The primary objectives of the study are to evaluate the safety and tolerability of the Humacyte HAV in PAD patients undergoing above-knee femoro-popliteal bypass surgery and to determine the patency (primary, primary assisted and secondary) rate of the Humacyte HAV at 24 months. Secondary objectives include assessment of the PRA and IgG response to the HAV and to

assess patency (primary, primary assisted and secondary) at 6, 12 and 18 months, to determine the rates of interventions needed to maintain/restore patency in the HAV, to assess any effect of implantation on claudication, rest pain and ischemic ulcers and to assess any effect on ankle-brachial index (ABI).

The second PAD study of similar design, CLN-PRO-V004, is being conducted in the US with enrollment ongoing.

2.3.3.1 CLN-PRO-V002 Study Results (24 M)

Recruitment began in October 2013 and was completed in June 2014 with 20 patients implanted. Thirteen patients completed the 2 year follow up visit. Of the 7 patients terminating the study early, 3 died and 4 were withdrawn after occlusion of the HAV. None of the deaths were considered related to the investigational device or procedure.

Kaplan-Meier analyses in which deaths were censored revealed primary, primary assisted, and secondary patency probability rates of 79.2%, 79.0%, and 89.5% at Week 26, 63.3%, 63.2%, and 84.2% at Month 12, 63.3%, 63.2%, and 79.0% at Month 18, and 58.1%, 57.9%, and 73.7% at Month 24.

Six patients (30%) required at least 1 graft intervention to maintain or restore HAV patency during the study. Four patients required 1 intervention and 1 patient each required 3 and 4 interventions. Most interventions successfully restored patency. However, in 1 patient the graft patency could not be restored and the HAV was replaced with an alternative bypass graft. Two patients, who had previously undergone successful interventions, developed a recurrent thrombosis which was not treated and the HAV was left occluded. Two patients experienced HAV thrombosis with no or minimal symptoms and refused interventions on the HAV.

All 20 patients experienced AEs (a total of 92 events). Thirty-one of these events in 13 patients were considered serious. The most frequent AEs reported included graft thrombosis (35% of patients), anastomotic stenosis (20% of patients), lymphocele (20% of patients), and local swelling (15% of patient). Those serious adverse events (SAEs) reported by at least 2 patients were graft thrombosis (6 patients, 30%) and anastomotic stenosis (2 patients, 10%).

No patient showed an increase in PRA levels. Two patients had a significant (> 2 fold) increase from baseline in IgG levels. One of these patients experienced a thrombosis of the HAV between 3 and 6 months after implantation, while the other patient has had no HAV-related AEs and continues to have primary patency. Neither patient has had any evidence of dilatation or structural degeneration of the HAV.

2.3.4 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 8 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.

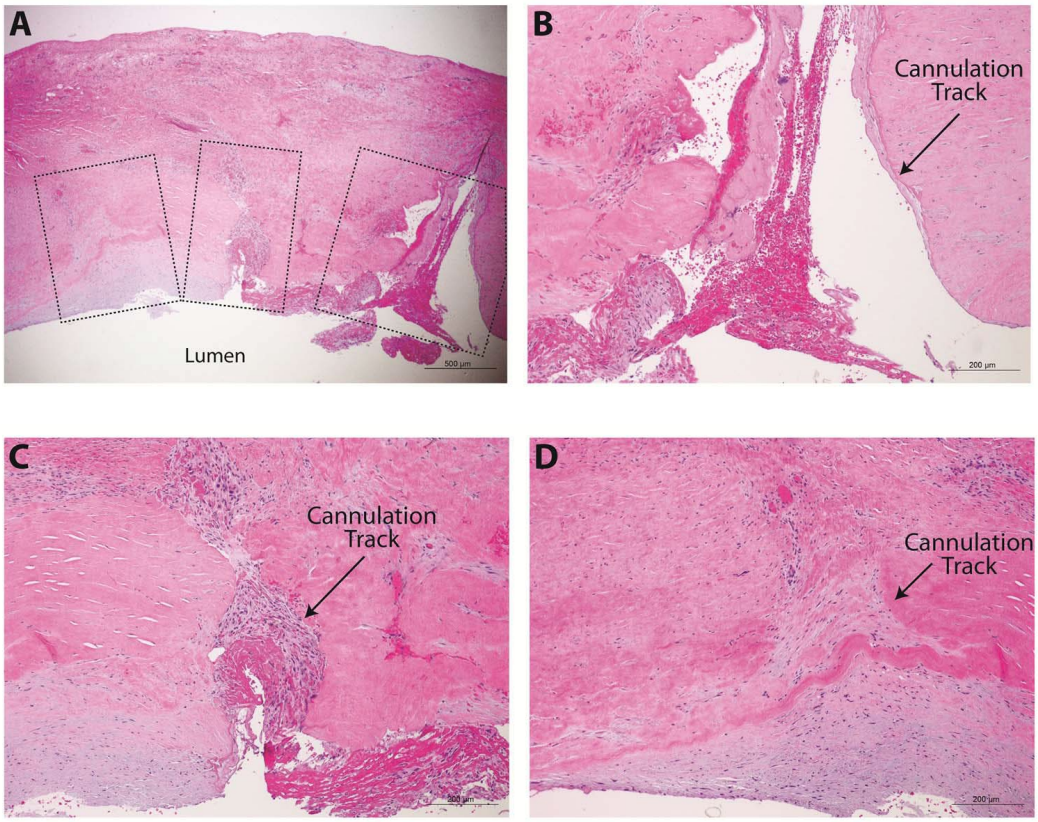
In these cases, small segments of the HAV and adjacent vascular tissue were explanted, fixed in formalin solution and shipped to Humacyte for analysis. Implant duration ranged from 16 to 55 weeks (median: 37 weeks).

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 1). In 1 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 1 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.

2.3.5 Conclusions

Clinical experience indicates that the HAV remains mechanically strong over implantation periods of more than 60 months with no evidence of dilatation. During more than 200 patient years of follow up across the 3 Phase 2 studies only 1 case of infection of the HAV material

itself has been reported. The SAE profile has been typical of that expected in the dialysis and PAD populations. In hemodialysis populations, secondary patency of the HAVs is substantially higher than the historical data for both ePTFE and AVF (accounting for non-maturation). In PAD, patency is in line with historical ePTFE and autologous conduit for above knee bypass. No evidence of immunogenicity of the HAV has been found and the HAV remains mechanically robust even after repeated puncture for hemodialysis and under high pressure, high outflow resistance in arterial reconstruction.

These data support the use of HAV in future Phase 2 and phase 3 studies for vascular replacement and reconstruction in diseased or damaged (trauma) vessels.

2.4 Study Design Rationale

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

Any significant safety or immunogenicity concerns with the HAV would likely be apparent in a short time frame after implant. Thus, the initial study analysis will be conducted after all subjects have reached 3 months post-implant. However, all subjects will be followed for 12 months and those with a patent HAV will continue follow up to 36 months to monitor for any potential long-term safety concerns with the Luna product.

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 may include, but are not limited to, the following:

- Aneurysm or pseudo-aneurysm formation
- HAV rupture
- Bleeding and hematoma formation at the surgical site or the dialysis puncture sites
- Thrombosis/occlusion of the HAV or host vessels

- Stenosis of the HAV or its anastomoses
- Infection of the HAV, 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 has been 1 reported aneurysmal dilatation of the HAV in Phase 2. The superficial site of implantation of the HAV 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 evaluate the safety, efficacy and immunogenicity over 3 months after implantation of HAVs manufactured using the commercial manufacturing system (Luna).

3.2 Secondary Objective

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

4. STUDY DESIGN

4.1 Description of the Study Design

This is a Phase 2, prospective, multicenter, open-label, single-arm study. Subjects who sign informed consent would undergo study-specific screening assessments within 45 days from the day of informed consent.

Eligible study subjects will receive a HAV and will be followed to 12 months post-implantation at routine study visits regardless of patency status. After 12 months, subjects with a patent HAV will be followed (while the HAV remains patent) for up to 3 years (36 months) post-implantation at study visits every 6 months.

4.2 Study Endpoints

4.2.1 Safety Endpoints

4.2.1.1 Primary Safety Endpoints – assessed at 3 months post implantation

- Adverse events indicating possible mechanical failure or weakness of the HAV
  - Anastomotic rupture
  - Anastomotic bleeding
  - Spontaneous HAV rupture
  - Aneurysm
  - Pseudoaneurysm
  - Abnormal post cannulation hemostasis
- HAV infections
- Change from baseline of PRA and anti-HAV IgG levels (at 2 months)
- All AEs/SAEs and adverse events of special interest.

4.2.1.2 Secondary Safety Endpoints – assessed throughout the 36 month post implantation follow-up

- Adverse events indicating possible mechanical failure or weakness of the HAV
  - Anastomotic rupture
  - Anastomotic bleeding
  - Spontaneous HAV rupture
  - Aneurysm
  - Pseudoaneurysm
  - Abnormal post cannulation hemostasis
- HAV infections
- Change from baseline of PRA and anti-HAV IgG levels (at 12 months)

- All AEs/SAEs until 12 months post implant, after that only SAEs associated with the HAV and adverse events of special interest.

4.2.2 Efficacy Endpoints

4.2.2.1 Primary Efficacy Endpoints – assessed at 3 months post implantation

- Primary patency
  - Defined as being maintained until any intervention designed to maintain or reestablish patency, access thrombosis or the measurement of patency', i.e., patent without interventions
- Primary assisted patency
  - Defined as being maintained until access thrombosis or the time of measurement of patency, including intervening manipulations (surgical or endovascular interventions) designed to maintain the functionality of patent access' i.e., patent without an intervention to clear a thrombus
- Secondary patency
  - Defined as being maintained until access abandonment
  - Access abandonment defined as no remaining segment of the study conduit is incorporated into the vascular access circuit used for dialysis

4.2.2.2 Secondary Efficacy Endpoints – assessed throughout the 36 month post implantation follow-up

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

4.3 Duration of Study Participation

Each subject will be followed at study specific visits until he/she has completed 12 months of follow-up after implantation (irrespective of patency status). After 12 months, subjects with a patent HAV will be followed (while the HAV remains patent) for up to 3 years (36 months) post-implantation at study visits every 6 months.

The expected duration of the clinical investigation is 40 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) for hemodialysis therapy.
2. Already established on hemodialysis
3. At least 18 years of age at Screening.
4. Suitable arterial and venous 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 45 days).
6. Other hematological and biochemical parameters within a range consistent with ESRD prior to Day 0 (within 45 days).
7. Normal clotting (international normalized ration [INR] ≤ 1.5 or prothrombin time ≤ 18 sec unless the patient is taking an anticoagulant for an approved indication at the time of HAV implantation.
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 HAV 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 as defined as either:
    a. a biochemical diagnosis (e.g. Factor V Leiden, Protein C deficiency, etc.) - OR –
    b. a clinical history of thrombophilia as diagnosed by 2 or more spontaneous intravascular thrombotic events (e.g deep vein thrombosis, pulmonary embolism, etc.) within the 5 previous years.
6. Spontaneous or unexplained bleeding diathesis clinically documented within the last 5 years or a biochemical diagnosis (e.g. von Willebrand disease, etc.).
7. Active clinically significant immune-mediated disease, not controlled by maintenance immunosuppression.
    a. Low dose glucocorticoid therapy (e.g. up to 10 mg 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 HAV 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 1 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 HAV.
14. Previous enrollment in this study or any other study with HAV.
15. Employees of Humacyte and employees or relatives of the investigator.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Human Acellular Vessel

6.1.1 Product Description

The IMP is Humacyte's 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 has an inner diameter of 6 mm and approximately 42 cm in length (~40 cm of usable length). The product is supplied on a silicone mandrel immersed in sterile, phosphate buffered saline with the bioreactor bag in which it was grown and decellularized, and this sterile bioreactor bag is sealed within a labeled plastic Peel Pak® container with Tyvek lid.

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

The IMP that was administered to subjects in Humacyte's Phase 3 studies was produced by a contract manufacturing organization (AlloSource, Centennial, CO) using a bioreactor system capable of producing 10 HAV in a single batch. Humacyte has constructed a commercial manufacturing facility in Durham, North Carolina and has installed bioreactor systems in this new plant capable of producing 200 HAV in a batch. The fundamental aspects of the manufacturing process have remained unchanged. Human smooth muscle cells are seeded onto a tubular scaffold composed of poly-glycolic acid contained within a bioreactor container. Tissue culture medium is circulated through the bioreactor system that encourages growth of the cells within the scaffold. A cyclic, pulsatile force is delivered through the lumen of the tubular scaffold that causes the smooth muscle cells to secrete extracellular matrix proteins, resulting in a 3 dimensional tissue-engineered construct. Cellular material is removed from this construct by treatment with various chemical treatments, resulting in an acellular tubular implant that is contained in the bioreactor housing immersed in buffered saline solution. The commercial manufacturing systems have incorporated highly advanced process controls and automation in comparison with the previous systems used at AlloSource. However, HAV produced in the new plant in North Carolina using the larger scale commercial equipment will be shown to be biochemically and mechanically comparable to HAV produced previously prior to administration to subjects in this study.

6.1.2 Manufacturer of the Investigational Medicinal Product

The HAV is manufactured by:

Humacyte, Inc.
2525 E. Highway 54
Durham, NC 27713

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.

The HAV product unit is fixated within the box in a custom designed, thermoformed tray, with fittings to hold the tubing at either end and constrain the HAV product unit. A Tyvek lid material is then heat sealed to the top perimeter external surface of the tray to completely enclose the HAV product unit. The vessel container is stored and shipped in an opaque, non-corrugated, lacquer- coated cardboard outer box. The box prevents light penetration and its surfaces are non- shedding. The product is stored and shipped under controlled conditions validated to maintain temperature at approximately 4°C (range: 2 – 10°C).

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 and/or instructions for use document packaged with HAV 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 and/or instructions for use document packaged with HAV for details).

6.2 Investigational Medicinal Product Accountability Procedures

6.2.1 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 Shipment Confirmation Form. Once signed, the 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. 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.

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 electronic case report form (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 concomitant medications taken during the study, only medication name, indication for use and start and stop dates will be recorded in the eCRF. Only prescription medications plus aspirin (including any combination drug containing aspirin) will be captured.

7.2 Essential and Restricted Medications

7.2.1 Essential Medications

All subjects should receive both antibiotic and antithrombotic therapy in conjunction with HAV 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: This is not a requirement, but if heparin is used, the 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 HAV (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, prothrombin time [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 -45 to Day 0)

The screening period time window is currently specified as a maximum of 45 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. Patients 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 Independent Ethics Committee (IEC) approved consent form. The informed consent will cover:

- Agreement to participate in the trial for the full 3 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 HAV 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). All conditions

for which the subject is currently taking medications or receiving ongoing therapies are considered a present condition and should be listed.

8.1.4 Prior and Concomitant Medications

All prescription medications and aspirin that the subject is taking during the study or has taken within 7 days prior to surgery must be recorded 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 PEs 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, glucose (non-fasting).
- Coagulation: INR or PT (if INR value is not available)
- PRA
- Anti-HAV IgG antibodies

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 HAV 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 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 HAV is planned is identified/suspected, it must be corrected before implantation.

8.1.10 Review of Subject Eligibility

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

8.1.11 Serious Adverse Events

Only 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 Surgical Placement of the HAV (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 Subject Eligibility

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 implantation.

8.2.4 Surgical Placement

The surgical procedure for implantation, including the location of the HAV, and any complications immediately postoperatively must be documented indicating whether subject remained in the hospital the night after surgery. If so, it has to be recorded 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 HAV will be confirmed intraoperatively or immediately post-surgery by the investigator's preferred method (eg. PE, Doppler, ultrasound, etc.) and will be documented in the source documents and recorded in the eCRF.

8.2.6 Adverse Events

The subject will be asked general questions about his/her health and for any HAV 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

Changes in all concomitant prescription medications and aspirin use since last visit will be documented in the source documents and recorded in the eCRF

8.3.2 Symptom-directed Physical Examination, including Temperature

A symptom-directed PE (if needed) including subject's temperature will be performed. 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 source documents and recorded in the eCRF Clinical Examination of HAV

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

8.3.4 Assessment of Problems with the Access Site or HAV and HAV Interventions

Any problems and interventions with the access site and HAV including infections and the occurrence of thrombosis must be documented. Any procedures performed or treatments, including reasons for the procedures and dates of hospitalization, will be documented in the source documents and recorded in the eCRF.

8.3.5 Assessment of HAV Patency and Flow

The patency of the HAV and adequacy of flow will be assessed by the investigator using the investigator's preferred method (eg. palpation, stethoscope auscultation, Doppler, ultrasound, etc.) and will be documented in the source documents and recorded in the eCRF.

8.3.6 Assessment of Hemodialysis and Placement and/or Removal of Central Venous Catheter

Information on subject hemodialysis since the last study visit, including frequency will be documented in the source documents and recorded in the eCRF. Additionally, information on CVC in place or if the subject had a CVC in place since the last visit will be documented in the source documents and recorded in the eCRF. Of particular interest is whether an alternate route for dialysis (CVC, peritoneal) is used and for how long.

8.3.7 Assessment of Adverse Events

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

8.3.8 Assessment of Events of Special Interest

Events of Special Interest are defined in Section 9.3, 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 9.2), whether or not causally related to the IMP, the event must be reported by the investigator to 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 3 years post-implantation. This information may 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 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

Changes in all concomitant prescription medications and aspirin use will be documented in the source documents and recorded in the eCRF.

8.4.2 Symptom-directed Physical Examination, including Temperature

Perform a symptom-directed PE (if needed) including 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 HAV

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

8.4.5 Assessment of any Problems with Access Site or HAV and HAV Interventions

Any problems and interventions with the access site and HAV including infections and the occurrence of thrombosis must be documented. Any procedures performed or treatments, including reasons for the procedures and dates of hospitalization, will be documented in the source documents and recorded in the eCRF.

8.4.6 Assessment of HAV Patency

The patency of the HAV 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 HAV patency, diameter of the lumen mid-conduit, implant and anastomotic stenosis, volumetric flow rate, and to monitor for true aneurysm development. The full length of the HAV should be visualized with particular attention paid to any increase in diameter of the conduit that might indicate aneurysm formation. For purposes of this study, the full length of the HAV constitutes the entire conduit and includes both arterial and venous anastomoses. The methodology will be described in the study manual.

8.4.8 Determination that the HAV may be used for Dialysis

Beginning on Day 28 post-implantation (± 7 days), the investigator (or designee) should evaluate the HAV to determine if it is suitable to be used for dialysis. Such suitability will be recorded in the eCRF and transmitted to the dialysis center caring for that subject with guidance that cannulation of the HAV for dialysis should not start before 28 days post-implantation (earlier use of the HAV for dialysis for urgent clinical reasons may be permitted but must be approved prospectively by the medical monitor).

If the HAV is deemed not ready for use, either the subject should be brought back to the site for a repeat assessment in a few weeks, or an intervention arranged.

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

Information on subject hemodialysis since the last study visit, including frequency will be documented in the source documents and recorded in the eCRF. Additionally, information on CVC in place or if the subject had a CVC in place since the last visit will be documented in the source documents and recorded in the eCRF. 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 HAV 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 9.3. 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, glucose (non-fasting).
- PRA
- Anti-HAV IgG antibodies

8.5 Postoperative Evaluations (Month 2 to Month 12)

8.5.1 Evaluations and Procedures to be performed at All Study Visits from Month 2 to Month 12

The following assessments will be performed at the Month 2 (± 7 days), Month 3 (± 7 days), Month 6 (± 14 days), and 12 (± 14 days), visits:

8.5.1.1 Concomitant Medications

All concomitant prescription medications and aspirin taken during the study up to Month 12 will be recorded in the eCRF.

8.5.1.2 Symptom-directed Physical Examination, including Temperature

Perform a symptom-directed PE (if needed) including 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 HAV

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

8.5.1.4 Assessment of HAV Patency

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

8.5.1.5 Assessment of any Problems with the Access Site and HAV and Interventions, Including Events of Special Interest

Any problems and interventions with the access site and HAV including infections and the occurrence of thrombosis must be documented. Any procedures performed or treatments, including reasons for the procedures and dates of hospitalization, will be documented in the source documents and recorded in the eCRF.

Subjects should be assessed for the occurrence of Events of Special Interest as defined in Section 9.3. Detailed information about each of these events will be recorded in the eCRF as described in Section 8.3.9. If the HAV is abandoned, the reason for abandonment will be documented in the eCRF.

8.5.1.6 Duplex Ultrasound

A duplex ultrasound will be performed to assess HAV 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 HAV should be visualized with particular attention paid to any increase in diameter of the HAV that might indicate aneurysm formation.

8.5.1.7 Determination that the HAV may be used for Dialysis (if not previously approved)

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

8.5.1.8 Assessment of Hemodialysis and Placement and/or Removal of CVC

Information if the subject underwent hemodialysis since the last study visit, including frequency will be documented in the source documents and recorded in the eCRF. Additionally, information if the subject has a CVC in place or if the subject had a CVC in place since the last

visit will be documented in the source documents and recorded in the eCRF. Of interest is whether an alternate route for dialysis (CVC, peritoneal) is used and for how long.

8.5.1.9 Assessment of Adverse Events

The subject will be asked general questions about his/her health and for any HAV 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 12

8.5.2.1 Removal of CVC that was in place Pre-implantation: Month 2 and 3

The date and reason for removal of the CVC that was in place pre-implantation, if applicable, will be documented in source data and recorded in eCRF.

8.5.2.2 PRA and Anti-HAV IgG Antibodies: Month 2, 6, and 12

A blood sample will be collected for the PRA and Anti-HAV IgG antibodies evaluation.

8.5.2.3 Laboratory Data: Month 2

At Month 3 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, glucose (non-fasting)

8.6 Long Term Follow Up Post Month 12 through Month 36 Evaluations and Procedures

After 12 months, only subjects with a patent HAV will be followed for up to 3 years (36 months) post-implantation at study visits every 6 months.

8.6.1 Evaluations and Procedures that will be performed at All Study Visits Post Month 12 to Month 36 (± 1M)

8.6.1.1 Symptom-directed Physical Examination, including Temperature

Perform a symptom-directed PE (if needed) including 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.

8.6.1.2 Clinical Examination of Access Site and HAV

A clinical examination of the access site and HAV will be performed at all post Month 12 study visits.

8.6.1.3 Assessment of HAV Patency

The patency of the HAV 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.). This assessment is not required for HAV that have been abandoned.

8.6.1.4 Assessment of any Problems with the Access Site or HAV and Interventions, Including Events of Special Interest

Any problems and interventions with the access site and HAV including infections and the occurrence of thrombosis must be documented. Any procedures performed or treatments, including reasons for the procedures and dates of hospitalization, will be documented in the source documents and recorded in the eCRF.

Subjects should be assessed for the occurrence of Events of Special Interest as defined in Section 9.3. Detailed information about each of these events will be recorded in the eCRF as described in Section 8.3.9. If the HAV is abandoned, the reason for abandonment will be documented in the eCRF.

8.6.1.5 Determination that the HAV may be used for Dialysis (if not previously approved)

The investigator should evaluate the HAV to determine if it is suitable to be used for dialysis. Such suitability needs to be recorded in the eCRF and transmitted to the dialysis center caring for that subject.

8.6.1.6 Assessment of Hemodialysis and Placement and/or Removal of CVC

Information if the subject underwent hemodialysis since the last study visit, including frequency will be documented in the source documents and recorded in the eCRF. Additionally, information if the subject has a CVC in place or if the subject had a CVC in place since the last visit will be documented in the source documents and recorded in the eCRF. Of particular interest is whether an alternate route for dialysis (CVC, peritoneal) is used and for how long.

8.6.1.7 Duplex Ultrasound

A duplex ultrasound will be performed to assess HAV 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 HAV should be visualized with particular attention paid to any increase in diameter of the HAV that might indicate aneurysm formation.

8.7 Early Termination Visit

If a subject discontinues from the study before the Month 36 visit, then every effort should be made to perform the following early termination (ET) visit assessments:

- Patients withdrawn prior to Month 12 should complete an ET that correlates with the procedures at Month 12.
- Patients withdrawn after Month 12 and prior to Month 36 should complete an ET visit that correlates with procedures post Month 12 through Month 36.

8.7.1 Concomitant Medications (if prior to month 12)

Any changes to the subject's prescription medications and aspirin use will be documented in source data and recorded in eCRF.

8.7.2 Symptom-directed Physical Examination, including Temperature

Perform a symptom-directed PE (if needed) including 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.

8.7.3 Clinical Examination of the Access Site and HAV

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

8.7.4 Assessment of HAV Patency

The patency of the HAV 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 Assessment of any Problems with the Access Site or HAV and Interventions, Including Events of Special Interest

Any problems and interventions with the access site and HAV including infections and the occurrence of thrombosis must be documented. Any procedures performed or treatments, including reasons for the procedures and dates of hospitalization, will be documented in the

source documents and recorded in the eCRF.Subjects should be assessed for the occurrence of Events of Special Interest as defined in Section 9.3. Detailed information about each of these events will be recorded in the eCRF as described in Section 8.3.9. If the HAV 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 HAV 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 HAV should be visualized with particular attention paid to any increase in diameter of the HAV that might indicate aneurysm formation.

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

Information if the subject underwent hemodialysis since the last study visit, including frequency will be documented in the source documents and recorded in the eCRF. Additionally, information if the subject has a CVC in place or if the subject had a CVC in place since the last visit will be documented in the source documents and recorded in the eCRF. 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 HAV or dialysis problems since the previous visit. See Section 9 for information regarding AE collection and data handling.

8.7.9 PRA and Anti-HAV IgG Antibodies (if prior to month 12)

A blood sample to measure PRA and anti-HAV IgG antibody levels must be collected.

8.8 Collection and Processing of Laboratory Samples

Details concerning sample collection and processing can be found in the Study Manual.

9. SAFETY ASSESSMENTS AND ADVERSE EVENTS

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

- Anastomotic rupture
- Anastomotic bleeding
- HAV spontaneous rupture
- Aneurysm
- Pseudoaneurysm
- HAV infection
- Increase from baseline in PRA/Anti-HAV IgG antibodies
- Need for HAV revision or removal
- Other AEs
- Laboratory parameters (clinical chemistry and hematology)

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.

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 1 of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires removal or abandonment of the HAV
- The abnormality or test result is clinically significant in the opinion of the investigator.

9.2 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 HAV will not be considered an SAE. However, prolongation of the initial hospitalization due to an AE will be considered a SAE.

9.2.1 Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is any adverse drug reaction 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.

9.3 Events of Special Interest

Events of Special Interest related to interventions and infections will be evaluated and include the following:

- Events resulting in HAV abandonment
- HAV thrombosis
- HAV infection
- HAV aneurysm (HAV lumen diameter > 9 mm) formation
- Clinically significant HAV pseudoaneurysm (clinically significant defined as requiring a surgical or radiological intervention)
- HAV spontaneous rupture
    - Iatrogenic injuries are not an Event of Special Interest and should be reported as an AE
- Events resulting in HAV revision or ligation

- Events resulting in HAV removal
- Clinically significant stenosis of HAV (clinically significant defined as severity of severe or greater, or requiring a surgical or radiological intervention)
- Clinically significant Steal Syndrome (clinically significant defined as severity of severe or greater, or requiring a surgical or radiological intervention)
- Anastomotic bleeding
- Anastomotic rupture

9.4 Criteria for Determining Causal Relationship to the HAV and Criteria for Determining Casual Relationship to Index Surgical Procedure

The criteria for determining the causal relationship of an AE with the HAV is presented in the table below. A separate assessment of causal relationship of an AE to the HAV implantation procedure is required as well using the same criteria and definitions presented in the table below. Please note that causal relationship to procedure only refers to the index surgical procedure in which the HAV was initially implanted.

Causal Relationship to the HAV	**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 HAV 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 HAV). 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 HAV) 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 HAV or, another cause is obvious and in which there is sufficient information that the etiology of the event is not related to the HAV.

9.5 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.

9.6 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 -45 to Day 0 prior to implantation), only SAEs related to study procedures will be reported beginning at the time the subject signs the informed consent form. From Day 0 after implantation to 1 year post-implantation (Month 12 visit) or ET visit, whichever occurs earlier, all AEs will be reported.

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

- All related SAEs
- All Events of Special Interest (as defined in Section 9.3).

9.6.1 Reporting of Serious Adverse Events

Any SAE (as defined in Section 9.2) which occurs from Day 0 after implantation to 1 year post-implantation (Month 12 visit) or ET visit, whichever occurs earlier, whether or not causally related to the IMP, must be reported by the investigator to Humacyte or designee immediately (**no later than 24 hours after learning of its occurrence**). Any related SAE during the long-term follow-up period from 1 year to 3 years post-implantation must be reported by the investigator to Humacyte or designee immediately (**no later than 24 hours after learning of its occurrence**). Events of special interest should follow the same reporting time frame as SAEs.

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 (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 HAV.

Humacyte or Humacyte's designee will submit expedited safety reports to the regulatory agencies and IECs as necessary according to the timelines provided in the Safety Management Plan and will inform the investigators of such regulatory reports.

9.6.2 Monitoring and Reporting of Serious Adverse Events Not Related to the HAV

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

For those events identified as not being related to the HAV, Humacyte will monitor these events for any increase in frequency that may indicate a link to the HAV. Occurrences of non-HAV related SAEs will be excluded from expedited reporting to the applicable regulatory authorities and to IECs. If aggregate analysis of these events indicates they occur more frequently with the HAV than expected, an expedited safety report may be submitted.

9.6.3 Follow-Up of Adverse Events

If any AEs are present when a subject completes 1 year 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.

9.7 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 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 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.

9.8 Study Suspension and Stopping Criteria

All SAEs that may indicate acute HAV infection (<30 days post-implant), mechanical failure of the HAV, or inflammatory/immune response to the HAV will be notified within 72 hours to the DMC chair who will consider whether a formal review of study continuation should be undertaken. The DMC chair will respond to Humacyte regarding the need for a safety review within 48 hours. If such a review is deemed necessary by the DMC chair recruitment into the study will be placed on hold until that review is complete. The sites will be notified by fax or e-mail of any such hold on recruitment.

9.9 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established to review safety on an ongoing basis and to provide recommendations about stopping, continuing or otherwise modifying the study. The DMC will consist of individuals who are not directly involved in the conduct of the study. The DMC will review data from this study on an ongoing basis with the 1st scheduled DMC review after the last patient completes Month 3 and every 6 months thereafter. A separate charter will be established that will describe the roles and responsibilities of the DMC. Responsibilities of the DMC will include review of aggregate safety data from other studies in the HAV clinical development program.

9.10 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 and IECs.

10. STATISTICAL CONSIDERATIONS

This is a prospective, two center, open label, single arm study with no formal hypothesis testing. Data will be summarized using descriptive statistics only.

All available data will be summarized and reported in a Clinical Study Report (CSR) when the last patient completes 3 months of follow up. A second analysis will be conducted when all patients have completed 12 months of follow up. The final analysis will occur when the final patient completes 36 months of follow up. Details of data handling and planned descriptive statistics are in the Statistical Analysis Plan.

11. STUDY MANAGMENT 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), as per International Conference on Harmonization (ICH) E6 guidelines. 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.

Personal subject data will be kept confidential in compliance with the European Union General Data Protection Regulation 2016/679 and other applicable international and national requirements.

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 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 obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information.

11.3 Independent Ethics Committee

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 IEC to his/her 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 letter from the IEC stating that the membership list is on file, must be obtained from the 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 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 IEC. This includes notification to the 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 IEC, and submission of final study reports and summaries to the IEC.

11.4 Subject Informed Consent

Subjects must sign and date an 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 HAVs 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, GCP (ICH E6 guideline), and in accordance with any local regulations. The investigator (or designee such as the CRO) is responsible for the preparation, content and IEC approval of the informed consent document. The consent form must be approved by the site's 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 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 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.

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 2 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 2 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 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 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 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 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 3-month endpoint, a CSR 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 12 months, and then up to 36 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, 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 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 9.2 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, 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 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 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 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 -45 to D 0	**D 0**	**D7[9]**	**D 28**	**M 2**	**M 3**	**M 6**	**M 12**	**M 18-36 at 6M intervals**	**ET[10]**
Visit Window	--	--	+8 D	±7 D	±7 D	±7 D	±14 D	±14 D	±1 M	--
Informed consent	X									
Demographics	X									
Medical history	X	X								
Concomitant medications[1]	X	X	X	X	X	X	X	X		X
Physical exam and temperature[2]	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
ECG (12-lead)	X									
Vessel mapping[3]	X									
Assessment of central vein stenosis	X									
Confirmation of eligibility (inclusion/exclusion criteria)[4]	X	X								
Surgical placement of HAV and documentation of any complications		X								
Labs[5]	X			X	X					
PRA / anti-HAV IgG	X			X	X		X	X		X
Assessment of surgical site healing			X	X						
Clinical examination of access site and HAV			X	X	X	X	X	X	X	X
Documentation of problems with access site and HAV and interventions			X	X	X	X	X	X	X	X

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

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

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

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

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

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

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

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

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

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

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

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