# A Phase 2 Study for the Evaluation of Safety and Efficacy of Humacyte's Human Acellular Vessel for Use as a Vascular Prosthesis for Femoro-Popliteal Bypass in Patients with Peripheral Arterial Disease

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| Medicinal Product: | Humacyte Human Acellular Vessel (Humacyte HAV) |
| Study No.: | CLN-PRO-V004 |
| IND No: | 16,746 |
| Sponsor: | Humacyte, Inc. |
| Address: | 2525 East NC Highway 54 |
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| Phone: | 919-313-9633 |
| CRO: | Atlantic Research Group, Inc. |
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| | Charlottesville, VA 22903 |
| Version: | 4.0 (Amendment to version 3.0 dated 16 July 2018) |
| | 1 Oct 2020 |

## Confidentiality Statement

# STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol and the following regulatory 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 sections of United States Food and Drug Administration (FDA) Code of Federal Regulations (CFR), including:
    - 21 CFR Part 11, Electronic Records; Electronic Signatures
    - 21 CFR Part 50, Protection of Human Subjects
    - 21 CFR Part 54, Financial Disclosure by Clinical Investigators
    - 21 CFR Part 56, Institutional Review Boards
    - 21 CFR Part 312, Investigational New Drug Application

# PRINCIPAL INVESTIGATOR AGREEMENT PAGE FOR THE PROTOCOL

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 the sponsor, Humacyte, Incorporated (Humacyte), or their authorized representatives.

- Not to implement any deviations from or changes to the protocol (including protocol amendments) without agreement from the sponsor and prior review and written approval from the Institutional Review Board (and FDA, if applicable) except where necessary to eliminate an immediate hazard to the patient(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 the sponsor including, but not limited to the current Investigator Brochure or equivalent document provided by Humacyte.

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

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

Principal Investigator: _____

Name and Title

Signed: _____ Date: _____

# PROTOCOL APPROVAL

Sponsor Medical Approval: Kiernan DeAngelis, MD, VP Clinical, Humacyte Inc

Name and Title

Signed: _____ Date: _____

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| | |
|---|---|
| ABI | Ankle brachial index |
| AE | Adverse event |
| AIDS | Acquired immunodeficiency syndrome |
| aPTT | Activated partial thromboplastin time |
| AV | Arteriovenous |
| AVF | Autologous arteriovenous fistula |
| BUN | Blood urea nitrogen |
| CAVG | Canine acellular vascular graft |
| CT | Computed tomography |
| CM | Concomitant medication |
| eCRF | Electronic case report form |
| CRO | Contract research organization |
| DMC | Data Monitoring Committee |
| DTH | Delayed-type hypersensitivity |
| ECG | Electrocardiogram |
| ECM | Extracellular matrix |
| EDFMV | Endothelium-dependent flow-mediated vasodilation |
| ePTFE | Expanded polytetrafluoroethylene |
| ESRD | End-stage renal disease |
| ET | Early termination |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HAV | Human Acellular Vessel |
| HCG | Human chorionic gonadotropin |
| HIV | Human immunodeficiency virus |
| IB | Investigator Brochure |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IgG | Immunoglobulin G |
| IHC | Immunohistochemistry |
| IMP | Investigational medicinal product |
| INR | International normalized ratio |

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| IRB | Institutional Review Board |
| ISO | International Organization for Standardization |
| IU | International unit |
| IV | Intravenous |
| LMWH | Low molecular weight heparin |
| MedDRA | Medical Dictionary for Regulatory Activities |
| M | Month |
| N | Number (typically refers to participants) |
| NYHA | New York Heart Association |
| OTC | Over-the-counter |
| PAD | Peripheral arterial disease |
| PE | Physical examination |
| PI | Principal Investigator |
| PORF | Pregnancy & Outcome Report Form |
| PRA | Panel reactive antibodies |
| PTFE | Polytetrafluoroethylene |
| RBC | Red blood cells |
| RMST | Restricted mean survival time |
| SAE | Serious adverse event |
| SOP | Standard operating procedure |
| SUSAR | Suspected unexpected serious adverse reaction |
| SVS WIfI | Society for Vascular Surgery: Wound, Ischemia, and foot Infection |
| US | Ultrasound |
| USA | United States of America |
| WBC | White blood cell(s) |
| WOCBP | Women of child bearing potential |

# PROTOCOL SUMMARY

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| **Full Title** | A Phase 2 Study for the Evaluation of Safety and Efficacy of Humacyte's Human Acellular Vessel for Use as a Vascular Prosthesis for Femoro-Popliteal Bypass in Patients with Peripheral Arterial Disease |
| **Clinical Trial Phase** | Phase 2 |
| **Sponsor** | Humacyte, Inc. |
| **Planned Study Sites** | Up to 8 sites in the United States |
| **Sample Size** | Up to 25 patients |
| **Study Population** | Patients with peripheral arterial disease (PAD) |
| **Inclusion Criteria** | 1. Patients with disabling symptomatic peripheral arterial disease<br>a. Rutherford stage 4 or 5 who require femoro-popliteal bypass surgery or<br>b. Rutherford stage 3 with severe claudication (less than 50 yards AND causing severe impairment of ability to work or undertake social activities)<br>2. Ankle – brachial index (ABI) ≤ 0.6 in the study leg<br>3. Patient has failed adequate medical therapy which included<br>a. Exercise program<br>b. Smoking cessation therapy<br>c. Control of diabetes, hypertension and dyslipidemias<br>d. Antiplatelet therapy<br>4. Preoperative angiography or computed tomography (CT) angiography shows superficial femoral artery occlusion AND required Humacyte Human Acellular Vessel (HAV) length of ≤ 38 cm. This imaging may have been conducted up to 6 months prior to study entry (Day 1) provided that the patient's symptoms have remained stable since that time<br>5. Preoperative imaging shows at least one below knee vessel patent to the ankle with good runoff |

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| | 6. Proximal HAV anastomosis is expected to be to the common femoral artery below the inguinal ligament or to the superficial femoral artery<br>7. Distal anastomosis is expected to be to the popliteal artery above the knee<br>8. Femoral artery occlusion is not considered suitable for endovascular treatment; e.g. long segment chronic total occlusion, previous failed stent or stent graft in the superficial femoral artery, previous failed endovascular treatment where the lesion could not be crossed<br>9. Autologous vein graft is not feasible in the judgment of the treating surgeon; e.g. because all suitable veins have been used previously for coronary or peripheral bypass, or pre-operative vein mapping shows inadequate length or quality of vein to complete the planned bypass<br>10. Aged 18 to 85 years old, inclusive<br>11. Hemoglobin ≥ 10 g/dL and platelet count ≥ 100,000/$mm^3$ at screening<br>12. Other hematological and biochemical parameters within a range considered acceptable for the administration of general anesthesia at screening<br>13. Adequate liver function, defined as serum bilirubin ≤ 1.5 mg/dL; and international normalized ratio (INR) ≤ 1.5 at screening<br>14. Able to communicate meaningfully with investigative staff, competent to give written informed consent, and able to comply with entire study procedures<br>15. Life expectancy of at least 1 year |
| **Exclusion Criteria** | 1. Leg at high risk of amputation (SVS WIfI stage 4)<br>2. Recent clinically significant trauma to the leg receiving the HAV<br>3. Severe active infection (SVS foot infection grade 3) in the leg receiving the HAV<br>4. Distal anastomosis planned to a below knee artery<br>5. History or evidence of severe cardiac disease (New York Heart Association [NYHA] Functional Class III or IV), myocardial infarction within six months prior to study entry (Day 1), ventricular tachyarrhythmias requiring continuing treatment, or unstable angina<br>6. Stroke within six (6) months prior to study entry (Day 1) |

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| | 7. Chronic renal disease such that multiple administrations of contrast agents may pose an increased risk of nephrotoxicity (eGFR < 45 mL/min)<br>8. Uncontrolled diabetes (HbA1c >10% at screening)<br>9. Treatment with any investigational drug or device within 60 days prior to study entry (Day 1)<br>10. Cancer that is being actively treated with a cytotoxic agent<br>11. Acquired immunodeficiency syndrome (AIDS) / human immunodeficiency virus (HIV) infection<br>12. Documented hypercoagulable state as defined as either:<br>a) a biochemical diagnosis (e.g. Factor V Leiden, Protein C deficiency, etc.) - OR -<br>b) a clinical history of thrombophilia as diagnosed by 2 or more spontaneous intravascular thrombotic events (e.g. DVT, PE, etc.) within the previous 5 years<br>13. Spontaneous or unexplained bleeding diathesis clinically documented within the last 5 years or a biochemical diagnosis (e.g. von Willebrand disease, etc.).<br>14. Ongoing treatment with vitamin K antagonists or oral direct thrombin inhibitors or factor Xa inhibitors (e.g. dabigatran, apixaban or rivaroxaban)<br>15. Previous arterial bypass surgery (autologous vein or synthetic graft) in the operative leg<br>16. Stenosis of > 50% of the inflow aortoiliac system ipsilateral to the index leg. Any such stenosis must be corrected with angioplasty with or without stenting prior to, or at the time of, HAV implantation<br>17. Active autoimmune disease – symptomatic or requiring ongoing drug therapy<br>18. Active local or systemic infection (white blood cells [WBC] > 15,000/$mm^3$)<br>19. Known serious allergy to aspirin<br>20. Any other condition which in the judgment of the investigator would preclude adequate evaluation of the safety and efficacy of the Humacyte Human Acellular Vessel (HAV)<br>21. Previous exposure to HAV<br>22. Employees of the sponsor or patients who are employees or relatives of the investigator |

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| | 23. Pregnant women or women planning to become pregnant (Women of child bearing potential [WOCBP] must use adequate contraception [hormonal or barrier method of birth control; abstinence] for the duration of study participation; WOCBP defined as not sterile or not > 1 year postmenopausal.) |
| **Expected Enrollment Start** | 4 Q 2016 |
| **Accrual Period** | 36 months |
| **Study Duration** | The active study duration for each study participant will be 60 months from HAV implantation. The total expected duration of the clinical investigation is 97 months. |
| **Study Design** | Prospective, multicenter, single arm, non-randomized study |
| **Investigational Product/Intervention Description** | Patients will be implanted with a HAV as a femoro-popliteal bypass conduit using standard vascular surgical techniques. |
| **Primary Objectives** | **Safety**<br>● To evaluate the safety and tolerability of the Humacyte HAV in PAD patients undergoing femoro-popliteal bypass surgery<br>**Efficacy**<br>● To determine the patency (primary, primary assisted and secondary) rate of the Humacyte HAV at Month 12<br>● To determine the incidence of hemodynamically significant stenosis (> 70%) defined by duplex ultrasound, and the time to stenosis development |
| **Secondary Objectives** | **Safety**<br>● To assess changes in the panel reactive antibodies (PRA) response after HAV implantation<br>● To determine mechanical stability of the HAV based on freedom from aneurysmal degeneration on duplex ultrasound and CT imaging |

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| | ● To determine HAV durability in terms of freedom from need for HAV explantation or replacement due to infection, bleeding, or conduit degeneration<br><br>**Efficacy**<br>● To determine the patency of the HAV (primary, primary assisted and secondary) at Months 3, 6 and 9<br>● To determine the rates of interventions needed to maintain / restore patency in the HAV through Month 12<br>● To assess effect of HAV implantation on symptoms of PAD using the VascuQol instrument<br>● To assess effect of the HAV on ABI<br>● To assess effect of the HAV on 6 minute walk test |
| **Endpoints** | Endpoints will be assessed over a period of up to 60 months after HAV implantation. The primary analysis of the study will be conducted on the earlier of a) when the final subject enrolled reaches 12 months post-implant or b) all subjects enrolled in the initial 36 month accrual period have reached 12 months post-implant.<br><br>**Primary Endpoints:**<br>● Incidence of HAV aneurysm formation (true or pseudo)<br>● Anastomotic bleeding or spontaneous rupture<br>● HAV infection<br>● HAV removal<br>● Significant local inflammation at the HAV implantation site<br>● Frequency and severity of adverse events<br>● HAV patency rates (i.e., primary, primary assisted, and secondary)<br>● Hemodynamically significant stenosis (> 70% using duplex ultrasound criteria)<br><br>**Secondary Endpoints:**<br>● Change from baseline in PRA<br>● Change from baseline in hematology, coagulation, and clinical chemistry parameters |

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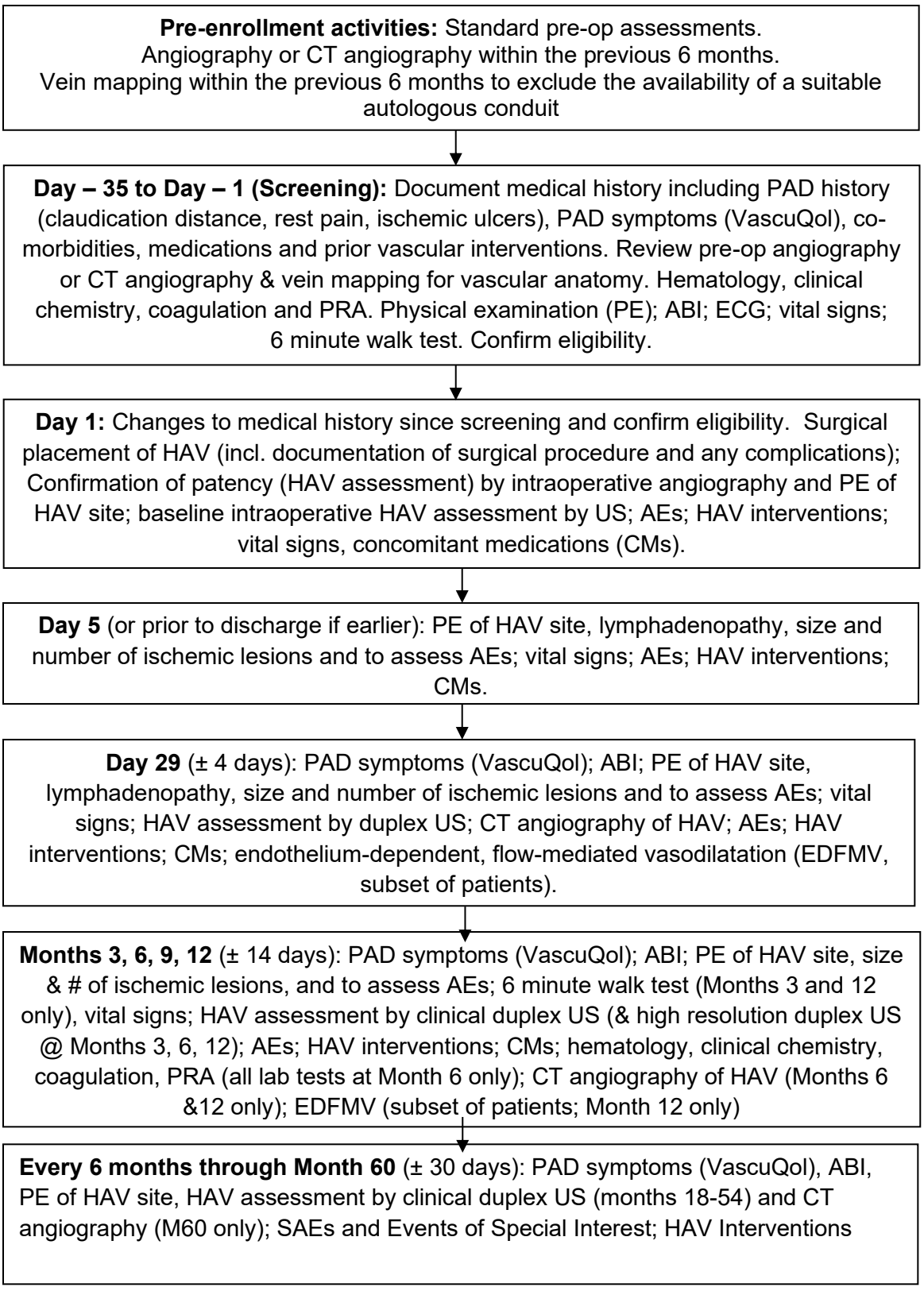
| | ● HAV interventions<br>● Patient reported PAD symptoms (VascuQol)<br>● ABI<br>● 6 minute walk test<br>● HAV remodeling at Months 1 (Day 29), 6 and 12 by CT angiography and US<br><br>**Long Term Endpoints (post Month 12 through 60): (to be evaluated at specified study visits):**<br>● HAV interventions<br>● Evidence of aneurysmal dilatation or stenosis of the HAV on routine clinical duplex US<br>● Primary, primary assisted, and secondary patency at 18, 24, 30, 36, 42, 48, 54 and 60 months<br>● Limb salvage/amputation at 18, 24, 36, 48, and 60 months, for all subjects who have not died, withdrawn, or been lost to follow-up.<br>● Incidence of surgical revascularization of the implanted limb, at the level of the HAV or distal to HAV, for all patients who have not died, withdrawn, or been lost to follow-up.<br>● VascuQol PAD symptom assessment consists of 25 questions. The total score and the 5 domain scores (Activity, Symptom, Pain, Emotional, and Social) will be recorded in the clinical database, at 18, 24, 36, 48 and 60 months, for all patients who have not died, withdrawn, or been lost to follow-up. |
| **Protocol Approval (Version and Date)** | Version 4.0 (1 Oct 2020) |

**Schematic of Study Design**: (obtain informed consent prior to any study-specific activities)



# 1. STUDY PERSONNEL

An updated list of all study personnel will be maintained by the CRO. Protocol amendments will not be required for staff changes at Humacyte, the CRO or the sites (except change of Principal Investigator at a site).

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# 2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## 2.1. Background Information

Peripheral arterial disease (PAD), involving atherosclerosis with complete or partial occlusion of blood vessels in the peripheral circulation, is a major cause of morbidity and mortality in the developed world. It is estimated to affect between 8 and 12 million people in the United States of America (USA) (Criqui, 1997). In many patients, peripheral arterial disease is asymptomatic and its importance lies mainly as a marker of generalized atherosclerosis and the associated high risk of myocardial infarction and stroke (Hirsch, 2001). Peripheral arterial disease may however cause disabling symptoms, progressing from intermittent claudication which limits mobility, to rest pain and ultimately to critical ischemia of the limb necessitating amputation.

In many patients, the disease can be managed effectively with medical therapy including antiplatelet agents and statins, and an exercise program to increase exercise tolerance. However, in more severe disease a range of techniques have been developed to improve or restore blood flow to the affected limb. Depending on the anatomical location and extent of the atherosclerotic lesions, percutaneous procedures such as angioplasty and stenting may be effective to reopen blocked vessels. However, for long segment stenosis and occlusions, bypass grafting with autologous vein or synthetic grafts such as polytetrafluoroethylene (PTFE) or Dacron™ may be required (Norgren, 2007; Conte, 2015). The long-term success of these procedures, particularly those using synthetic grafts, is limited by early thrombotic occlusion and by later neo-intimal hyperplasia leading to stenosis at the anastomoses. In addition, infection is a common occurrence associated with synthetic grafts. This additional hazard is compounded by the difficulties frequently encountered with antibiotic treatment of these infections.

There is thus a need for alternative conduits which more closely mimic human vascular tissue, that may avoid or reduce the complications associated with PTFE and Dacron.

## 2.2. Scientific Rationale

Humacyte, Inc. (Humacyte) has developed an acellular, human collagen-based vessel (Human Acellular Vessel – HAV) to provide an alternative to synthetic materials and to autologous grafts for the creation of vascular access for dialysis and for use in peripheral vascular bypass surgery. Because this product mimics native vascular tissue, it may possess the advantages of an autologous graft as well as the off-the-shelf availability benefit of synthetic grafts. Use of an off-the-shelf product avoids the surgical morbidity associated with vein graft harvest and, most

importantly, allows vessel bypass surgery in patients who have no suitable veins available. Because the product mimics native vessel, it may not have the compliance mismatch associated with synthetic alternatives. In addition, pre-clinical studies in pigs, canines and primates have shown that the HAVs resist intimal hyperplasia at the anastomoses (Quint, 2011, Prichard, 2011, Dahl, 2011). Upon implantation, it is anticipated (based on pre-clinical studies) that the collagen matrix comprising the HAV will be infiltrated with host cells and remodeled by the host. This could result in a vascular structure that is more similar to the histological composition of the native vascular tissue that may improve HAV longevity and be less likely to become infected.

## 2.3. Summary of Nonclinical Information

The nonclinical testing program was designed to comprehensively address:

- local and systemic effects of the product in multiple in vivo animal models acutely and chronically,
- functional aspects of product implanted into animal models as an arteriovenous conduit,
- biocompatibility of the HAV material in standardized in vitro and in vivo test protocols.
- Overall, the results of these studies indicated that the HAV extracellular matrix (ECM) material was non-toxic, well tolerated, and met standards for biocompatibility. Generally, the HAVs functioned as intended and maintained patency during the implantation period. (See the Investigator Brochure [IB] for a detailed summary of nonclinical data.)
- Pre-implantation, the HAV has mechanical properties (burst pressure and suture retention strength) comparable with native human artery and vein (**Table 1**). There was no evidence that HAV strength deteriorated after long-term implantation into baboons.

### Table 1: Summary of Mechanical Properties of Explanted Acellular Vessels

[a] From L'Heureux et al, *Nature Medicine*, 2006. (L'Heureux, 2006)

| Test Material | Burst Pressure (mm Hg) | Suture Strength (g) |
|---|---|---|
| Pre-Implant Humacyte HAVs | 3415 ± 1011 (n=4) | 180 ± 44 (n=12) |
| Post-Explant Humacyte HAVs | 3669 ± 1305 (n=5) | 276 ± 84 (n=11) |
| Human Saphenous Vein | 1,680 – 2,273[a] | 196 ± 2 (n=7)[a] |
| Human Artery | 2,031 – 4,225[a] | 200 ± 119 (n=9)[a] |

In the chronic animal testing, Humacyte grafts produced using canine cells were implanted into 12 canines (canine acellular vascular graft, CAVG) and 14 baboons (HAV) in a variety of anatomical locations. In general, the Humacyte vessels were safe and well tolerated and functioned as intended.

Mechanical failure was not observed in any HAV. Calcification was not observed in any CAVG or HAV. No graft exhibited hemodynamically significant intimal hyperplasia. Unlike with PTFE graft implantation, no evidence of systemic infection attributable to implantation of HAV was observed in any of the animals. One HAV developed an aneurysm that was resected and did not harm the animal. The HAV material showed no evidence of toxicity in hematology, clinical chemistry, and necropsy data. The HAVs could be accessed by venipuncture, and hemostasis was achieved following needle puncture.

On microscopic analysis, the HAVs were found to be well integrated into the host tissue. Overall, the cellular host response to the HAVs demonstrated smooth muscle actin-positive cells within the vessel wall, endothelial cells lining the lumen, and an adventitial-like outer layer adjacent to the vessel. These findings indicate that implanted HAVs were populated with cell types that are characteristic of healthy native vasculature. Examination of the anastomotic sections showed that the HAVs were well integrated with adjoining vasculature with minimal intimal hyperplasia observed. Furthermore, immunohistochemistry (IHC) was employed to identify CD-68 positive macrophages in the venous intimal tissue. Studies have shown a substantial macrophage population has been observed within venous intimal tissue adjacent to inflammatory PTFE arteriovenous grafts (Kelly, 2002, Roy-Chaudhury, 2001). Only sparse CD-68 positive macrophages were observed, indicating that the degree and the aggressiveness of the intimal hyperplasia associated with the HAV were less than that typically associated with PTFE grafts (Prichard, 2011).

Over time, the organization and composition of ECM components indicated that, aided by infiltration of host vascular cells, HAVs were remodeled in vivo in a manner that mimicked the dynamic remodeling process of native blood vessels. Given the difficulties associated with the baboon animal model, where mismatches in vein versus graft diameter were encountered and animals perturbed their wounds postoperatively, an overall assisted patency rate of approximately 80% (11/14) was achieved. In a xenogeneic transplant model that did not employ immunosuppression, the HAV material did not elicit biologically significant cellular or delayed-type hypersensitivity (DTH) immune responses. All animals developed immunoglobulin G (IgG) titers to the HAV material that did not appear to detrimentally impact vessel function.

In internationally recognized in vitro and in vivo International Organization for Standardization (ISO) test protocols, the HAV material met criteria for biocompatibility required of medical devices.

These data collectively support the safety of the HAV for the proposed clinical investigation.

## 2.4. Summary of Clinical Studies

### 2.4.1. Overview

The HAV clinical development program currently includes 8 clinical studies: 5 in patients with end-stage renal disease (ESRD) receiving hemodialysis (CLN-PRO-V001, CLN-PRO-V003, CLN-PRO-V006, CLN-PRO-V007, and CLN-PRO-V011), 2 in patients with PAD (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 and CLN-PRO-V005) and one Phase 3 study (CLN-PRO-V007) are open for enrollment. One Phase 2 study has completed enrollment and primary analysis is ongoing (CLN-PRO-V011).

As of 20 February 2020, 392 patients (330 ESRD patients, 35 PAD patients, and 27 vascular trauma 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 523 patient-years in the hemodialysis access population and 81 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.

### 2.4.2. Experience in Peripheral Arterial Bypass Patients

Humacyte has two 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 PAD. Pre-operative imaging (angiography or computed tomography [CT] angiography) must have demonstrated at least two 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 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 (AEs), and the HAV was examined using duplex ultrasound (US) 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 panel reactive antibodies (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.

### 2.4.3. 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 seven patients terminating the study early, three died and four 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.

**CLN-PRO-V002 Conclusions:**

- Humacyte HAV was safe and well tolerated in PAD patients.
- The HAV is able to withstand long term use in a high pressure, high outflow resistance arterial circuit.
- Patency rates for the HAV are within the ranges of patency rates of synthetic and autologous grafts presented in the literature.
- Humacyte HAV was not immunogenic.

### 2.4.4. Experience in Hemodialysis Patients

Two Phase 2 trials, one in Poland (CLN-PRO-V001) and one in the US (CLN-PRO-V003) have completed enrollment. Both recruited subjects requiring hemodialysis access for ESRD whom were not suitable for creation of an autologous arteriovenous fistula (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 two 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 ECM 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. Preliminary Month 18 results are presented below. 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 CLN-PRO-V007; however, blinded safety data is presented in the IB. A Phase 2 study of ESRD patients in Poland (CLN-PRO-V011) has primary assessments ongoing, and no safety or efficacy information is currently available.

### 2.4.5. 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 two 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 (AV) graft aneurysm was reported in Study CLN-PRO-V001 (moderate in intensity, considered possibly related to the investigational medicinal product [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 one or more renal transplant failures; one subject recently; one subject developed septic shock about a month before the elevated value; and the third subject, who was severely debilitated with a decubitus ulcer, died approximately a month after HAV abandonment.

IgG titers increased in 5 subjects; in 4 cases, the IgG titer increased and then decreased while the HAV remained functional with no clinical evidence of an inflammatory response; in one case the IgG titer increase occurred in a subject who maintained primary patency.

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

- 1 transplant (known to be functioning well at 12 months post-transplant)
- 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 two studies in dialysis access has been pooled for a combined Kaplan Meier analysis (Lawson, 2016). Based on these Kaplan-Meier plots, the patency at 6, 12 and 24 months is estimated to be 60%, 26% and 15% (primary patency) and 97%, 89% and 77% (secondary patency).

### 2.4.6. CLN-PRO-V006 Preliminary Study Results (18 M)

Details of Study CLN-PRO-V006 can be found in the IB. The CLN-PRO-V006 study was designed to enroll a broad range of ESRD patients in whom a clinical decision has been made to implant a 'graft' to provide vascular access for hemodialysis. The trial was limited to adults (≥18 years old), and subjects were either on hemodialysis or expected to start dialysis within 12 weeks of conduit implantation. The standard synthetic graft implanted in this clinical setting is an ePTFE graft (6 mm by 40 mm, straight, standard wall, non-stretch, and non-tapered).

The primary objective of the study is to compare the secondary patency of the HAV with that of the ePTFE graft when used as a conduit for hemodialysis. Key secondary objectives of the study are to compare the primary patency of the HAV with that of the ePTFE graft (efficacy) and to compare the rate of access-related infections for the HAV with that of the ePTFE graft (safety).

A summary of losses of secondary patency (events) for ePTFE and HAV are shown in Table 2. At 6 and 12 months post-implantation, the HAV arm had 9 and 6 fewer losses, respectively, of secondary patency than the ePTFE arm. At 18 months, the ePTFE arm had 4 fewer losses of secondary patency than the HAV arm.

**Table 2 Summary of Secondary Patency Losses - ITT Set**

| Time Point | Number of ePTFE Patency Losses | ePTFE Kaplan-Meier Probability of Patency | Number of HAV Patency Losses | HAV Kaplan-Meier Probability of Patency |
|---|---|---|---|---|
| 6 Months | 21 | 88.0% | 13 | 92.3% |
| 12 Months | 33 | 80.7% | 29 | 81.8% |
| 18 Months | 37 | 77.6% | 41 | 73.0% |

ePTFE=expanded polytetrafluoroethylene; HAV=Human Acellular Vessel; ITT=Intent to Treat

The CLN-PRO-V006 Statistical Analysis Plan pre-specified the use of the Cox Proportional Hazards model to compare the secondary patency rates of HAV and ePTFE. The observed hazard ratio for loss of secondary patency at 18 months is 1.19, with lower and upper 95% confidence interval (CI) of 0.78 and 1.81, respectively. Since the observed upper 95% CI is greater than the non-inferiority margin, we failed to reject the null hypothesis, and therefore, could not establish non-inferiority of HAV relative to ePTFE.

However, given that the hazards for loss of secondary patency between HAV and ePTFE were not proportional (i.e., the curves for secondary patency cross near 400 days, making the relative risks of loss of patency non-proportional over time), the pre-specified Cox Proportional Hazards model is not ideally suited to analysis of the CLN-PRO-V006 secondary patency data. Therefore, a sensitivity analysis was performed using the non-parametric restricted mean survival time (RMST) method, which does not make assumptions regarding proportionality of hazards between the two arms of the trial. RMST estimates a gain or loss in the event-free survival time due to treatment versus control in a specified time period. The results from the RMST analysis indicated that the time to failure of secondary patency was delayed, on average, by 11 days in the HAV arm compared to the ePTFE arm at the 18 month time point, and non-inferiority of the HAV in comparison to ePTFE was demonstrated with this alternative RMST analysis.

The time to loss of primary patency was significantly shorter for the HAV than for ePTFE, with a hazard ratio of 1.89. Since losses of primary patency for the HAV seemed to briefly accelerate around 60 to 90 days, it is unclear the extent to which study-mandated ultrasounds at 60 and 90 days, combined with the lack of experience in managing the HAV at most study sites, may have triggered interventions on the HAV study conduit that would have led to a loss of primary patency at those times.

Information on access-related infections was collected for all study subjects. Table 3 provides the rates of access-related infections involving the study conduit (not local site infections, and not infections of tunneled dialysis catheters or other accesses). The HAV had significantly fewer study access-related infections than ePTFE (p= 0.041), with the absolute rate of infections for ePTFE roughly five times higher than HAV (4.76 vs. 0.97 infections per 100 subject years of dialysis use for ePTFE and HAV, respectively). Fewer HAV subjects required intravenous antibiotics for treating their access related infections. Markedly fewer HAV subjects required hospitalization for infection (13 vs. 3 instances of hospitalization for infection with ePTFE and HAV, respectively). Lastly, conduit removals were more frequent for ePTFE than for HAV.

**Table 3 Summary of Access-Related Infections in V006**

| Clinical Event | ePTFE (N = 178) | HAV (N = 177) | Total (N = 355) |
|---|---|---|---|
| **Conduit Infections per 100 subject-years of dialysis** | 4.76 | 0.97 | (*p*=0.041) |
| **Subjects Needing IV Antibiotics** | 15 | 9 | 24 |
| **Subjects Needing Hospitalization** | 13 | 3 | 18 |
| **Conduit Removals (partial and complete)** | 8 | 13 | 21 |

ePTFE = expanded polytetrafluoroethylene, HAV = Human Acellular Vessel, IV = intravenous

### 2.4.7. 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 (Kirkton, 2019). 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 16 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 200 weeks.

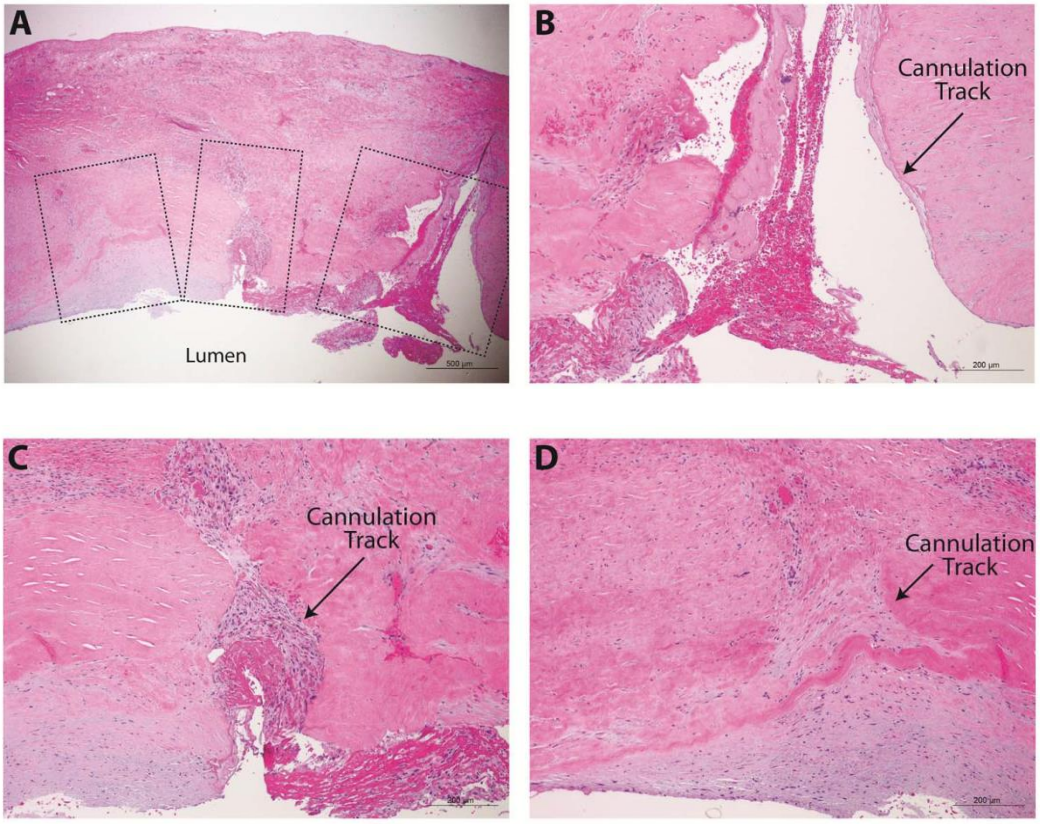
In man, the HAV remodeled in a manner consistent with that observed in primate studies. There was infiltration of cell populations that are normally associated with angiogenesis and vascular organization and structure; namely, those with endothelial, smooth muscle and fibroblastic phenotypic characteristics 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 one case, an explanted specimen was tested for suture retention strength at the time of explant and exhibited a substantial increase over the pre-implant level.

**Figure 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 image above shows a mid-vessel segment explanted at 11 months post-implant and shows several prior cannulation tracts from dialysis access. Figure 1B shows a very recent cannulation site with fresh clot extending into the tract from the lumen. Figure 1C 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.

### 2.4.8. Conclusions

Clinical experience indicates that the HAV remains mechanically strong over implantation periods of more than 60 months with no evidence of dilatation. The HAV profile includes use as a hemodialysis access in ESRD subjects, an arterial bypass conduit in PAD and vascular trauma subjects, and an interposition vessel in vascular trauma subjects. The benefit-risk for the HAV remains favorable in these subject groups and continued clinical development for these target indications is warranted. 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.

## 2.5. Potential Risks and Benefits

### 2.5.1. Potential Risks

It is anticipated that subjects participating in the study will be exposed to similar risks to those associated with other arterial conduits. Risks associated with the study investigational product may include but are not limited to:

- Thrombosis/occlusion of the conduit or host vessels, with consequent limb ischemia
- Embolism from a thrombosed conduit

- Bleeding and hematoma formation at the surgical site
- Infection – at the surgical site or systemic
- Stenosis of the conduit or its anastomoses
- Aneurysm or pseudoaneurysm formation
- Swelling of the limb

Regular clinical examination of the HAV implantation site and assessment of the patency, blood flow and diameter using ultrasound during the study should allow early detection of complications and permit appropriate intervention including HAV explantation. CT angiography at Months 1, 6, 12 and 60 will allow the detection of anatomical abnormalities of the HAV such as localized dilation and intimal hyperplasia.

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

### 2.5.2. Potential Benefits

Patients who undergo implantation of the Humacyte HAV may benefit from a reduced number of infections and infection-related complications versus a conventional ePTFE or a Dacron graft. In addition, the risks listed in Section 2.5.1 typically encountered with conventional synthetic grafts may be decreased with the Humacyte HAV. Finally, the longevity (secondary patency) of the Humacyte HAV may be greater than that of conventional synthetic grafts.

### 2.5.3. Risk-Benefit Rationale

The risks anticipated in this study are similar to those associated with currently marketed prosthetic grafts used for peripheral bypass surgery. The potential advantages of the HAV compared to currently marketed grafts may lead to a lower infection rate and reduced need for HAV replacement.

Recruitment will be restricted to a maximum of 25 subjects who receive implants to provide safety and efficacy data in the PAD population.

There is no formal hypothesis testing in this study, but data from the study will be compared with historical data on synthetic peripheral bypass grafts to assess the safety and efficacy of the HAV.

# 3. STUDY OBJECTIVES

## 3.1. Primary Objectives

This is an open label Phase 2 study. There is no formal hypothesis testing.

**Safety:**

- To evaluate the safety and tolerability of the Humacyte HAV in PAD patients undergoing femoro-popliteal bypass surgery

**Efficacy:**

- To determine the patency (primary, primary assisted and secondary) rate of the Humacyte HAV at Month 12
- To determine the incidence of hemodynamically significant stenosis (>70%) defined by duplex ultrasound, and the time to stenosis development

## 3.2. Secondary Objectives

**Safety:**

- To assess changes in the PRA response after HAV implantation
- To determine mechanical stability of the HAV based on freedom from aneurysmal degeneration on duplex ultrasound and CT imaging
- To determine HAV durability in terms of freedom from need for HAV explantation or replacement due to infection, bleeding or conduit degeneration

**Efficacy:**

- To determine the patency of the HAV (primary, primary assisted and secondary) at Months 3, 6 and 9
- To determine the rates of interventions needed to maintain / restore patency in the HAV through Month 12
- To assess effect of HAV implantation on symptoms of PAD using the VascuQol instrument
- To assess effect of the HAV on ABI
- To assess effect of the HAV on 6 minute walk test

# 4. STUDY DESIGN

## 4.1. Description of the Study Design

Prospective, multicenter, single arm, non-randomized Phase 2 study

## 4.2. Study Endpoints

Endpoints will be evaluated at multiple time points up to 60 months after HAV implantation. The primary analysis of the study will be conducted on the earlier of a) when the final subject enrolled reaches 12 months post-implant or b) all subjects enrolled in the initial 36 month accrual period have reached 12 months post-implant.

### 4.2.1. Primary Endpoints

**Safety:**

- Incidence of HAV aneurysm formation (true or pseudo)
- Anastomotic bleeding or spontaneous rupture
- HAV infection
- HAV removal
- Significant local inflammation at the HAV implantation site
- Frequency and severity of adverse events

**Efficacy:**

- HAV patency rates (primary, primary assisted, and secondary patency rate)
- Hemodynamically significant stenosis (>70% by duplex ultrasound criteria)

### 4.2.2. Secondary Endpoints

**Safety:**

- Change from baseline in PRA
- Change from baseline in hematology, coagulation, and clinical chemistry parameters

**Efficacy:**

- HAV interventions
- Patient reported PAD symptoms (VascuQol)
- ABI
- 6 minute walk test
- HAV remodeling at Months 1 (Day 29), 6 and 12 by CT angiography and US

### 4.2.3. Long Term Endpoints (post Month 12 through Month 60)

- HAV interventions
- Evidence of aneurysmal dilatation or stenosis of the HAV on routine clinical duplex US
- Primary, primary assisted, and secondary patency at 18, 24, 30, 36, 42, 48, 54 and 60 months
- Limb salvage/amputation at 18, 24, 36, 48, and 60 months, for all subjects who have not died, withdrawn, or been lost to follow-up.
- Incidence of surgical revascularization of the implanted limb, at the level of the HAV or distal to HAV, for all patients who have not died, withdrawn, or been lost to follow-up.
- VascuQol PAD symptom assessment consists of 25 questions. The total score and the 5 domain scores (Activity, Symptom, Pain, Emotional, and Social) will be recorded in the clinical database, at 18, 24, 36, 48 and 60 months, for all patients who have not died, withdrawn, or been lost to follow-up.

## 4.3. Duration of Study Participation

For an individual subject, the expected duration of active study participation is approximately 61 months. Enrollment (accrual) is expected to occur over 36 months. Additional data on patient and HAV status will be collected at 6 month intervals through 60 months after HAV implantation.

# 5. STUDY POPULATION

## 5.1. Description of the Study Population

The study population will consist of patients with symptomatic peripheral vascular disease as evidenced by claudication, rest pain or critical limb ischemia, who are being considered for femoro-popliteal bypass surgery.

### 5.1.1. Patient Inclusion Criteria

1. Patients with disabling symptomatic peripheral arterial disease
    a. Rutherford stage 4 or 5 who require femoro-popliteal bypass surgery or
    b. Rutherford stage 3 with severe claudication (less than 50 yards AND causing severe impairment of ability to work or undertake social activities)
2. ABI ≤ 0.6 in the study leg
3. Patient has failed adequate medical therapy which included
    a. Exercise program
    b. Smoking cessation therapy
    c. Control of diabetes, hypertension and dyslipidemias
    d. Antiplatelet therapy
4. Preoperative angiography or CT angiography shows superficial femoral artery occlusion AND required Humacyte HAV length of ≤ 38 cm. This imaging may have been conducted up to 6 months prior to study entry (Day 1) provided that the patient's symptoms have remained stable since that time
5. Preoperative imaging shows at least one below knee vessel patent to the ankle with good runoff
6. Proximal HAV anastomosis is expected to be to the common femoral artery below the inguinal ligament or to the superficial femoral artery
7. Distal anastomosis is expected to be to the popliteal artery above the knee
8. Femoral artery occlusion is not considered suitable for endovascular treatment; e.g. long segment chronic total occlusion, previous failed stent or stent graft in the superficial femoral artery, previous failed endovascular treatment where the lesion could not be crossed
9. Autologous vein graft is not feasible in the judgment of the treating surgeon; e.g. because all suitable veins have been used previously for coronary or peripheral bypass, or pre-operative vein mapping shows inadequate length or quality of vein to complete the planned bypass
10. Aged 18 to 85 years old, inclusive
11. Hemoglobin ≥ 10 g/dL and platelet count ≥ 100,000/$mm^3$ at screening

12. Other hematological and biochemical parameters within a range considered acceptable for the administration of general anesthesia at screening
13. Adequate liver function, defined as serum bilirubin ≤ 1.5 mg/dL; and international normalized ratio (INR) ≤ 1.5 at screening
14. Able to communicate meaningfully with investigative staff, competent to give written informed consent, and able to comply with entire study procedures
15. Life expectancy of at least 1 year

### 5.1.2. Patient Exclusion Criteria

1. Limb at high risk of amputation (SVS WIfI [Society for Vascular Surgery: Wound, Ischemia, and foot Infection] stage 4)
2. Recent clinically significant trauma to the limb receiving the HAV
3. Severe active infection (SVS foot infection grade 3) in the limb receiving the HAV
4. Distal anastomosis planned to a below the knee artery
5. History or evidence of severe cardiac disease (New York Heart Association [NYHA] Functional Class III or IV), myocardial infarction within six months prior to study entry (Day 1), ventricular tachyarrhythmias requiring continuing treatment, or unstable angina
6. Stroke within six (6) months prior to study entry (Day 1)
7. Chronic renal disease such that multiple administrations of contrast agents may pose an increased risk of nephrotoxicity (eGFR < 45 mL/min)
8. Uncontrolled diabetes (HbA1c >10% at screening)
9. Treatment with any investigational drug or device within 60 days prior to study entry (Day 1)
10. Cancer that is being actively treated with a cytotoxic agent
11. Acquired immunodeficiency syndrome (AIDS) / human immunodeficiency virus (HIV) infection
12. Documented hypercoagulable 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. DVT, PE, etc.) within the previous 5 years
13. Spontaneous or unexplained bleeding diathesis clinically documented within the last 5 years or a biochemical diagnosis (e.g. von Willebrand disease, etc.)
14. Ongoing treatment with vitamin K antagonists or oral direct thrombin inhibitors or factor Xa inhibitors (e.g. dabigatran, apixaban or rivaroxaban)
15. Previous arterial bypass surgery (autologous vein or synthetic graft) in the operative limb
16. Stenosis of > 50% of the inflow aortoiliac system ipsilateral to the index leg. Any such stenosis must be corrected with angioplasty with or without stenting prior to, or at the time of, HAV implantation

17. Active autoimmune disease – symptomatic or requiring ongoing drug therapy
18. Active local or systemic infection (white blood cells [WBC] > 15,000/$mm^3$)
19. Known serious allergy to aspirin
20. Any other condition which in the judgment of the investigator would preclude adequate evaluation of the safety and efficacy of the Humacyte HAV
21. Previous exposure to HAV
22. Employees of the sponsor or patients who are employees or relatives of the investigator
23. Pregnant women or women planning to become pregnant (women of child bearing potential [WOCBP] must use adequate contraception [hormonal or barrier method of birth control; abstinence] for the duration of study participation; WOCBP defined as not sterile or not > 1 year postmenopausal.)

# 6. INVESTIGATIONAL MEDICINAL PRODUCT

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

## 6.1. Product Description

The investigational medicinal product (IMP) is a Humacyte human acellular vessel (HAV), which is a tissue-engineered vascular prosthesis for arterial bypass in patients with peripheral arterial disease. It is a sterile, non-pyrogenic acellular tubular vessel composed of human collagen types I and III and other extracellular matrix proteins, including fibronectin and vitronectin. The vessel is 6 mm in diameter and approximately 42 cm in length. The product is supplied on a silicone mandrel immersed in normal physiological saline in a sealed and labeled container.

There is no placebo or comparator control group in this study.

## 6.2. Manufacturer of the IMP

The HAV is manufactured by:

AlloSource
6278 S. Troy Circle
Centennial, CO 80111 USA

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

## 6.3. Packaging, Storage, and Labeling

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

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

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

## 6.4. Implantation of the Humacyte human acellular vessel (HAV)

The Humacyte HAV is implanted using standard vascular surgical techniques similar to placement of standard peripheral vascular prostheses (see study manual for details).

Tunneling of the HAV must be performed using a sheathed tunneler. During tunneling, the HAV should be handled by pulling on the Dacron cuff (see study manual for details)

After placement, HAV patency and integrity are checked by pressurizing the HAV. Prior to completion of surgery angiography is performed to confirm adequacy of the HAV anastomoses, HAV patency and peripheral runoff. The surgical site is closed using standard techniques.

Implantation of the HAV will be undertaken by qualified vascular surgeons experienced in peripheral arterial bypass surgery.

## 6.5. IMP Accountability Procedures

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

## 6.6. Assessment of Patient Compliance with IMP

Not applicable.

## 6.7. Prior and Concomitant Medications

Prior medications are defined as all prescription medications or non-prescription aspirin taken within 7 days (whether continuing or not) prior to Day 1. All prior and concomitant medications (including immediately pre-surgery and post-surgery medications) must be listed in the patient's medical record and recorded on the electronic case report form (eCRF). Drugs used during anesthesia should be recorded in the anesthesia records but should not be transcribed into the

eCRF. Patients should be questioned at each study visit concerning any new medications or changes in current medications. **Note: particular attention should be made to identify the use of antithrombotic or antiplatelet agents (e.g., aspirin, clopidogrel, prasugrel, direct thrombin inhibitors, factor Xa inhibitors, or vitamin K antagonists).**

For each medication taken, the following information will be collected:

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

## 6.8. Essential, Precautionary and Prohibited Medications

### 6.8.1. Essential Medications

All patients should receive both antibiotic and antithrombotic prophylaxis in conjunction with HAV implantation:

**Antibiotic prophylaxis:**

- All patients must have at least 1 day of antibiotic prophylaxis in accordance with local hospital guidelines. Longer antibiotic prophylaxis is at the discretion of the investigator.

**Antithrombotic prophylaxis:**

- Intraoperative heparin: up to 150 IU/kg unfractionated heparin during surgery.
- Further measures to prevent venous thromboembolism are at the discretion of the investigator and may include low molecular weight heparin (LMWH).
- If antiplatelet therapy was not ongoing at the time of surgery, it should be commenced as soon as possible post operatively. Antiplatelet therapy (usually dual therapy with aspirin 81 to 325 mg and clopidogrel 75 mg daily) should continue long term while the HAV is in place. Choice of an alternative antiplatelet regimen if the patient is unable to tolerate aspirin or clopidogrel is at the discretion of the investigator

### 6.8.2. Restricted Medications

Vitamin K antagonists, antiplatelet agents other than aspirin and clopidogrel, direct thrombin inhibitors and factor Xa inhibitors (e.g., dabigatran, apixaban and rivaroxaban) should be avoided unless essential for treatment of a medical condition arising postoperatively. In that case, consideration should be given to modification or cessation of antiplatelet therapy. Antiplatelet therapy should be restarted on cessation of these anticoagulant drugs.

# 7. STUDY PROCEDURES / EVALUATIONS

## 7.1. Clinical Evaluations Through Month 12

- Medical History: at screening and Day 1, from patient interview and medical records covering relevant past medical history with particular reference to peripheral arterial disease, prior surgical or percutaneous procedures for PAD, other cardiovascular disease and concurrent medical conditions. Failure of optimum medical therapy for PAD should be documented.
- Smoking history and smoking cessation therapy: at screening and Day 1
- PAD symptoms assessment: at screening and all follow up visits from Day 29 onward through Month 12 using the VascuQol instrument (Morgan MBF et al 2001)
- Review of medications: at all study visits; prescription medication and non-prescription aspirin from Day -7 onward (see Section 6.7). Particular attention should be paid to the identification of over-the-counter (OTC) medications containing aspirin.
- Physical Exam: full exam at screening and Month 12 visit or final study visit for early termination (ET). Focused vascular clinical examination of the operative limb (including any ischemic lesions) and HAV at all post-operative visits; physical exam for lymphadenopathy at Day 5 and Day 29; additional clinical exam as needed to evaluate AEs.
- ABI (supine after 5 minute rest): at screening and all follow up visits from Day 29 onward through Month 12
- 6 minute walk test: at screening and at Months 3 and 12
- Vital signs (temperature, heart rate and sitting blood pressure): at screening and all subsequent study visits through Month 12
- Adverse events: post-operatively on Day 1 and all subsequent study visits; the patient will be asked a general question about his/her health and for any HAV problems since the previous visit.
- Angiography / CT angiography: this is a standard part of the pre-operative assessment of PAD patients. Patients should not be considered for the study unless results of a recent (within the 6 months prior to the screening visit and with no significant clinical deterioration subsequently) study are available.
- Vein mapping: this is a standard part of the pre-operative assessment of PAD patients. Patients should not be considered for the study unless results of a recent (within the 6 months prior to the screening visit) are available and indicate the absence of a suitable conduit for autologous vein bypass grafting.
- CT angiography to assess HAV anatomy at Day 29 and Months 6 and 12
- Intraoperative angiography to assess anastomotic anatomy, patency and runoff

- Clinical duplex ultrasound: clinical assessment at all postoperative visits from Day 29 through Month 12 to assess HAV patency, mid HAV diameter and flow rate. The full length of the HAV should be imaged at each assessment to monitor for aneurysm development.
- High resolution duplex ultrasound intra-operatively and at Months 3, 6 and 12
- Endothelium-dependent, flow-mediated vasodilatation assessed by ultrasound (selected patients only at Day 29 and Month 12)
- Electrocardiogram (ECG; 12-lead): at screening
- Documentation of HAV interventions, surgical procedures and any complications immediately postoperatively through Month 12

## 7.2. Clinical Evaluations in Long Term Follow Up (Post Month 12 to Month 60)

- Focused vascular clinical exam of operative limb
- ABI (supine after 5 minute rest)
- SAEs associated with the HAV
- Events of Special Interest as defined in Section 8.4
- Documentation of HAV interventions
- PAD symptoms assessment: VascuQol instrument (Morgan MBF et al 2001)
- Clinical duplex ultrasound: clinical assessment at all long term follow up visits from Month 18 onward through Month 54 to assess HAV patency, mid HAV diameter and flow rate. The full length of the HAV should be imaged at each assessment to monitor for aneurysm development.
- CT angiography to assess HAV anatomy at Month 60

## 7.3. Laboratory Evaluations

### 7.3.1. Clinical and Research Laboratory Evaluations and Specimen Collection

The following parameters will be measured at screening and Month 6:

- Hematology: hemoglobin, hematocrit, red blood cells (RBC), WBC with differential, platelet count
- Clinical chemistry: sodium, potassium, calcium, blood urea nitrogen (BUN), creatinine, albumin, total bilirubin, glucose (non-fasting)
- Urine or serum human chorionic gonadotropin (HCG) pregnancy test for WOCBP defined as not sterile or not > 1 year postmenopausal (screening only)
- Coagulation: INR and activated partial thromboplastin time (aPTT)

- HbA1c (Screening only)
- PRA

All laboratory tests (except assay of PRA) will be conducted at certified hospital laboratories. Routine monitoring, maintenance or calibration of laboratory equipment is required per local site procedures. Samples for analysis of PRA will be shipped to Humacyte for analysis at a central laboratory.

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

## 7.4. Imaging Evaluations

### 7.4.1. CT angiography

At Day 29 and Months 6, 12, and 60 CT angiography of the Humacyte HAV will be obtained using a multi-detector (≥ 16-slice detector) CT scanner. CT angiography images of the entire HAV will be acquired in a craniocaudal direction with a slice thickness of ≤ 1 mm using a bolus-tracking technique to optimize contrast opacification with automated injection of iodinated contrast (iohexol or similar).

Details of the procedure and the method of assessment of the images by a core lab will be given in a separate Imaging Procedures Manual.

### 7.4.2. Duplex ultrasound

Clinical duplex ultrasound examinations will be performed at Day 29 and Months 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, and 54 and will follow standard bypass graft imaging protocols, including B-mode, power duplex and color duplex ultrasound imaging of the HAV with velocity spectral waveform analysis. The purpose of this clinical duplex ultrasound surveillance is to detect HAV stenosis and aneurysm development.

High-resolution duplex ultrasound imaging will be performed at Day 1 and Months 3, 6 and 12 to investigate the structural, mechanical and functional characteristics of the Humacyte HAV. This protocol will involve standard vascular lab imaging equipment and can be accomplished immediately following the clinical scan. The estimated additional scanning time is 15-20 minutes.

A subset of patients will also undergo endothelium-dependent flow-mediated vasodilation (EDFMV) testing of the HAV at Day 29 and Month 12. HAV diameter, time-averaged blood flow velocity and mean blood flow will be measured at baseline and during reactive hyperemia. The

percent change in HAV diameter during reactive hyperemia represents flow-mediated vasodilation, considered evidence of endothelial function.

Details of the procedure and the method of assessment of the images by a core lab will be given in a separate Imaging Procedures Manual.

## 7.5. Study Schedule

### 7.5.1. Screening (Day -35 to Day -1)

Potential study participants who are being considered for femoro-popliteal bypass surgery will be informed about the study and invited to participate. After explanation of the potential risks and benefits of the HAV and of the study procedures, written informed consent will be obtained. No study specific procedures may be performed prior to patient consent.

The following assessments will be performed within 35 days prior to surgery (Day 1):

- Informed consent
- Medical history
- Review of medical therapy for PAD (exercise program; antiplatelet therapy; management of diabetes, hypertension and dyslipidemias to current guidelines; smoking history and assistance with smoking cessation)
- PAD symptoms (VascuQol)
- Prior and concomitant medications (all prescription medications plus non-prescription aspirin)
- Full physical examination including number, size and location of ischemic lesions on the intended implant leg
- Evaluation of inclusion/exclusion criteria
- ABI – measured with patient supine after 5 minutes rest
- 6 minute walk test
- Vital signs (blood pressure, heart rate, temperature – oral, axillary or tympanic)
- Review of recent angiography / CT angiography (within previous 6 months and no significant clinical change since then) to confirm length of stenosis / occlusion of superficial femoral artery, length of required HAV and patency of run-off vessels
- Review of vein mapping to confirm absence of suitable autologous conduit
- ECG (12-lead)

- Laboratory testing
  - Hematology: full blood count and differential
  - Clinical chemistry; sodium, potassium, calcium, BUN, creatinine, albumin, total bilirubin, glucose (non-fasting)
  - Urine or serum HCG pregnancy test for WOCBP
  - Coagulation tests: aPTT and INR
  - HbA1c
  - PRA (sample to be taken for later analysis)

### 7.5.2. Enrollment – Day 1 (HAV Implantation)

Prior to surgery the following assessments will be performed:

- Medical history (change from screening)
- Medication history (change from screening)
- Physical exam including surgical site (and HAV patency), number, size and location of ischemic lesions on the implant limb, and to evaluate any AEs
- Confirmation of eligibility (all screening results reviewed)
- Vital signs (heart rate, blood pressure, temperature – oral, axillary or tympanic)
- Adverse events

Intraoperative Procedures:

- Implantation of HAV and documentation of surgical procedure, any complications (e.g., prolonged oozing at anastomoses), and interventions
- Confirmation of adequacy of anastomoses, patency and run-off by intraoperative angiography
- High-resolution duplex ultrasound of the HAV will be performed to provide a baseline for follow up measurements

### 7.5.3. Follow-up Visits Day 5 through Month 12

**Day 5 (or prior to hospital discharge if earlier)**

- Review of concomitant medications
- Physical exam including surgical site (and HAV patency); lymphadenopathy; number, size and location of ischemic lesions on the implant leg; and to evaluate any AEs
- Vital signs

- Documentation of any HAV interventions
- Adverse events

**Day 29 (± 4 days)**

- PAD symptoms (VascuQol)
- Review of concomitant medications
- Physical exam including surgical site (and HAV patency); lymphadenopathy; number, size and location of ischemic lesions on the implant leg; and to evaluate any AEs
- Clinical duplex ultrasound of the HAV
- EDFMV testing of the HAV (subset of patients) using high resolution duplex ultrasound
- CT angiography of HAV
- Documentation of interventions
- ABI – supine after 5 minutes rest
- Adverse events
- Vital signs

**Months 3, 6 and 9 (± 14 days)**

- PAD symptoms (VascuQol)
- Review of concomitant medications
- Physical exam including surgical site (and HAV patency); number, size and location of ischemic lesions on the implant leg; and to evaluate any AEs
- Vital signs
- ABI – supine after 5 min rest
- 6 minute walk test (Month 3 visit only)
- Clinical duplex ultrasound of the HAV
- High resolution duplex ultrasound of the HAV (Months 3 and 6 only)
- CT angiography of HAV (Month 6 only)
- Documentation of interventions
- Adverse events
- Laboratory assessments (clinical chemistry, hematology and coagulation, PRA) – all at Month 6 only

**Month 12 (±14 days) and Early Termination**

- PAD symptoms (VascuQol)
- Review of concomitant medications
- ABI – supine after 5 min rest
- 6 minute walk test
- Clinical and high resolution duplex ultrasound of the HAV
- EDFMV testing of the HAV (subset of patients) using high resolution duplex ultrasound
- CT angiography of HAV
- Documentation of interventions
- Adverse events
- Full physical exam including surgical site (and HAV patency); number, size and location of ischemic lesions on the implant leg; and to evaluate any AEs
- Vital signs

### 7.5.4. Long Term Follow Up Post Month 12 through Month 60 (± 30 days)

The status of the patient and HAV will be ascertained every 6 months through 5 years after HAV implantation.

- PAD symptoms (VascuQol)
- ABI – supine after 5 min rest
- Documentation of interventions
- SAEs
- Events of Special Interest as defined in Section 8.4
- Physical exam of HAV surgical site and distal limb
- Clinical duplex ultrasound of the HAV (Months 18 through Month 54)
- CTA of operative extremity (Month 60 only)

### 7.5.5. Early Termination Visit

The patient may withdraw from the study at any time at his/her own discretion. The treating physician may also withdraw the subject for safety reasons. If withdrawal occurs before Month 12, the patient will be asked to complete an early termination visit at which all assessments normally performed at Month 12 will be completed. If withdrawal occurs after Month 12 and prior to

Month 60, the patient will be asked to complete an early termination visit at which all assessments normally conducted during the long term follow up visits will be completed.

The reasons for early termination should be recorded in the eCRF.

### 7.5.6. Unscheduled Visits

If necessary to evaluate adverse events or HAV complications, additional visits may be scheduled at the discretion of the investigator. At a minimum, HAV status on clinical examination and Doppler ultrasound and adverse events will be recorded.

**If, at any of the scheduled visits, duplex ultrasound surveillance suggests the development of a ≥ 50% stenosis within the HAV but immediate intervention is not required, closer follow up should be considered. Intervention to manage any such stenosis is at the discretion of the investigator taking into account the degree and rate of progression of the stenosis.**

## 7.6. Medical Care during the Study and upon Study Termination

Optimal medical therapy should be continued during the study. This should include:

- An exercise program
- Smoking cessation advice and therapy
- Management of diabetes, hypertension and dyslipidemias according to current guidelines.
- Antiplatelet therapy (see Section 6.8.1)

After the final study visit at Month 60, patients will not receive any further study-specific treatment. They will be treated by their physician in a way that is appropriate for them.

## 7.7. Histological Examination of Resected HAV Material

If all or part of the HAV is resected, it should, wherever possible, be retained for future histological examination. Instructions for preservation, storage and shipping of this material will be provided separately in a procedures manual. If a patient dies with an HAV in situ and it is feasible to obtain a fresh postmortem sample of the HAV, this should be attempted in accordance with local regulations.

# 8. SAFETY ASSESSMENTS AND ADVERSE EVENTS

Safety of the HAV will be assessed in terms of:

- Aneurysm formation
- Pseudoaneurysm formation
- Anastomotic bleeding or spontaneous rupture
- HAV infection
- Need for HAV removal
- Significant inflammation at the implantation site
- Other adverse events
- Laboratory parameters (clinical chemistry, hematology, and coagulation)
- Increase from baseline in PRA

## 8.1. Adverse Event Definition

An AE is any untoward medical occurrence in a patient administered an IMP and which does not necessarily have a causal relationship with the IMP. An AE can, therefore, be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP. Any worsening of the patient's disease under study or other medical conditions will also be considered to be an AE, unless it is within the normal range of disease fluctuation for that patient.

## 8.2. Serious Adverse Event Definition

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

- Results in death
- Is life-threatening
    - The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not include an adverse event that had it occurred in a more severe form, might have caused death.

- Requires patient hospitalization or prolongation of existing hospitalization
    - This is defined as the patient being hospitalized for 24 hours or more or the patient's hospital stay being prolonged for at least an additional overnight stay.
- Requires intervention to prevent permanent damage
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important Medical Events
    - For the purpose of this study, this includes any event involving the HAV that results in a surgical or endovascular radiological intervention. The event(s) which caused the procedure should be reported as an SAE. For example: in the event of HAV thrombosis, the thrombosis would be considered the SAE; any associated stenoses (or other associated findings) that are present would be considered AEs.

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above. These may also be considered to be SAEs.

Note: Hospitalization for the surgery to implant the HAV is not a SAE. However, prolongation of the initial hospitalization due to an AE will be considered a SAE.

## 8.3. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is any adverse drug reaction that is serious (as defined in Section 8.2), unexpected (is not listed in the IB or is not listed at the specificity or severity that has been observed) and suspected (meaning there is a reasonable possibility that the IMP caused the adverse event).

## 8.4. Events of Special Interest

Events of Special Interest are:

- HAV occlusion (thrombosis)
- HAV spontaneous rupture

  - Iatrogenic injuries are not an Event of Special Interest and should be reported as an AE
- HAV infection
- HAV abandonment
- HAV aneurysm
- HAV pseudoaneurysm
- HAV excision (partial or complete)

## 8.5. Reporting of Adverse Events

At each evaluation, the investigator will determine whether any AEs have occurred. The patient will be questioned in a general way and no specific symptoms will be suggested. If any AEs have occurred, they should be documented in the patient's medical chart and recorded on the AE pages of the eCRF. If known, the diagnosis should be recorded in preference to the listing of individual signs and symptoms. All serious adverse events (SAEs should be reported to the Safety Contract Research Organization (CRO) within 24 hours from the time the investigator or study personnel first become aware of the event.

AE reporting begins from implantation of the HAV (the moment the patient undergoes anesthesia) and ends at the conclusion of the Month 12 or ET visit unless an unresolved AE is still being followed.

During the long term follow up period from post Month 12 through Month 60, only the following will be reported by the investigator:

- All SAEs
- All Events of Special Interest (Section 8.4)

### 8.5.1. Criteria for Determining Causal Relationship to the HAV and Criteria for Determining Causal Relationship to the Index Surgical Procedure

The criteria for determining the causal relationship of an AE with the HAV are presented in the table below. A separate assessment of causal relationship of an AE to the index surgical 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 IP** | **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 surgical 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 surgical 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 medications). Although an adverse event may rate only as "possible" soon after discovery, it can be flagged as requiring more information and later be upgraded to 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 surgical 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 HAV was not implanted; or, another cause is obvious and in which there is sufficient information that the etiology of the event is not related to the HAV. |

The sponsor will make the final determination of causality for the purposes of reporting to the regulatory authorities and to the Principal Investigators.

### 8.5.2. Criteria for Defining the Severity of an Adverse Event

Severity of 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. |

### 8.5.3. Reporting of Action Taken to Resolve AE

- None
- Lab tests / further evaluation
- Treatment required (specify if hospitalized)
- Patient withdrawn from study
- Other (specify)

### 8.5.4. Reporting the Outcome of the AE

- Recovered, with sequelae
- Recovered, without sequelae
- Ongoing
- Death

- Lost to follow-up

### 8.5.5. Reporting Serious Adverse Events

The urgency for reporting SAEs is 4-fold: (1) to facilitate discussion (and implementation, if necessary) by the sponsor and the investigator of appropriate follow-up measures, (2) to facilitate investigator reporting of unanticipated problems involving risk to human subjects to the institutional review board (IRB), (3) to facilitate the sponsor's rapid dissemination of information regarding AEs to other investigators/sites in a multi-center study, and (4) to enable the sponsor to fulfill the reporting requirements to the appropriate regulatory authority.

**Any SAE that occurs through Month 60, whether or not causally related to the IMP, must be reported by the investigator or designee to the Safety CRO within 24 hours of learning of its occurrence. This applies also to any AE that could affect the safety of the study participants or the conduct of the study.**

Information about an SAE will be collected and recorded on the SAE Report Form. The investigator must assess the relationship to the investigational product and any relevant procedure.

The investigators must complete the SAE Report Form in English, and **send the completed, signed form by fax or email (see below) IMMEDIATELY (at latest within 24 hours) after becoming aware of the SAE.**

Copies of relevant medical records (e.g., admission and/or discharge summary, laboratory reports and autopsy report), may also be submitted with the SAE form to clarify the circumstances surrounding the SAE(s). The entire medical records should **NOT** be sent with the SAE form.

**Atlantic Research Group, Inc.**

**Drug Safety Department**

**Fax: +1-866-851-9318**

**Email: Safety@atlanticresearchgroup.com**

**Phone: +1-888-619-3216**

The investigator will be requested to supply as much detailed information as possible regarding the SAE that is available at the time of the initial contact. The investigator should also complete missing or requested information and submit follow-up reports until the SAE has resolved or, in the case of permanent impairment, until the SAE has stabilized.

It is the responsibility of each Principal Investigator to promptly notify his/her IRB of all SAEs that are received by the Sponsor or designee and that occur at his/her institution in accordance with institutional practices.

The Safety CRO will inform the sponsor about all SAEs within 1 business day after receipt of the respective report from the investigator.

### 8.5.6. Reporting of Events of Special Interest

Events of Special Interest are defined in Section 8.4 and should be reported to the Safety CRO within 24 hours of learning of its occurrence. For each of these events detailed surgical notes (with illustrative diagram), including reason for and outcome of any intervention or abandonment, should be completed within 48 hours and uploaded to the clinical database.

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

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

### 8.5.7. Follow-Up of Adverse Events

If any AEs are present when a subject completes 1 year post implant (Month 12) 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. The investigator or his designee should make every effort 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.

## 8.6. Reporting of Pregnancy

If a study participant becomes pregnant during study participation, the participant will be withdrawn from the study and the event will be recorded as an adverse event in the eCRF. The

site will also collect information about the pregnancy on the Pregnancy & Outcome Report Form (PORF), which must be submitted to the Safety CRO within 1 business day of completion. Complications experienced during the pregnancy will be recorded as AEs in the eCRF.

The participant will be asked to report the outcome of the pregnancy to the site. The site should collect the available outcome information and provide an updated PORF to the Safety CRO within 1 business day of receipt. 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.

## 8.7. Data Monitoring Committee

A Data Monitoring Committee (DMC) will review safety on an ongoing basis and provide recommendations about stopping, continuing or otherwise modifying the study. The DMC consists of individuals who are not directly involved in the conduct of the study. A charter describes 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.

## 8.8. Interim Analysis and Stopping Criteria

This is a Phase 2 study with no formal interim analysis. Periodic reviews of safety data will be undertaken by the DMC with particular attention to events that might indicate structural failure of the HAV. Events that might have implications for already implanted HAVs and their possible removal - such as aneurysm formation (true or pseudo) or spontaneous rupture - will trigger a referral of the event urgently for DMC review

The DMC may recommend modification or early termination of the study for safety reasons.

# 9. STATISTICAL CONSIDERATIONS

This is a prospective, open label, single treatment arm, multicenter pilot study to evaluate the safety and efficacy of the HAV in patients with PAD undergoing femoro-popliteal bypass surgery. The primary objective of this study is to evaluate the safety and tolerability of the HAV in these patients and to determine the patency of the Humacyte HAV at 12 months post-implantation. The secondary objectives of this study are to further assess safety in terms of PRA response, and to determine the rates of HAV interventions required to keep the HAV patent. There is no formal hypothesis testing planned; the study involves only a single, open-label treatment group.

Endpoints will be assessed over a period of up to 60 months after HAV implantation. The primary analysis of the study will be conducted on the earlier of a) when the final subject enrolled reaches 12 months post-implant or b) all subjects enrolled in the initial 36 month accrual period have reached 12 months post-implant. Details of data handling and planned descriptive statistics are given in the Statistical Analysis Plan.

## 9.1. Analysis Population

All patients who receive an HAV will be included in the analyses. For discontinued or withdrawn patients, all available data will be included in the safety and efficacy analyses.

## 9.2. Safety Analyses

Safety analyses will be performed on all patients who have an HAV implanted when the final patient enrolled reaches 12 months post-implant

Incidence of HAV aneurysm formation (true or pseudo), anastomotic bleeding or spontaneous rupture, HAV infection, HAV removal, and significant local inflammation at the HAV implantation site will be separately tabulated and listed.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terms. Adverse events will be listed and summarized by system organ class, preferred term, incidence, severity, and duration. HAV complications will be listed in terms of incidence, severity, and (where appropriate) time to onset and duration. Serious adverse events will be summarized separately. Any premature discontinuations due to adverse events and deaths will be listed and summarized.

Laboratory data, including PRA, will be listed and summarized using appropriate descriptive statistics at each visit and for the absolute change from baseline values for all post-surgery visits. The closest non-missing values prior to surgery on Day 1 will be used as baseline values.

## 9.3. Efficacy Analyses

Primary, primary assisted, and secondary patency rates of the HAV at Month 12 and at all other post-surgery visits with evaluation of patency will be described.

Primary patency is defined as the functional patency until any type of intervention; primary assisted patency is defined as an HAV still working without thrombosis; secondary patency is defined as the functional patency, with or without preceding successful interventional or surgical procedures to maintain or reestablish patency, until either final failure or the access is abandoned. Early discontinued patients prior to the visit of interest will be determined as being non-patent irrespective of the reason for discontinuation.

The rate and type of interventions needed to maintain / restore patency in the HAV will be descriptively tabulated.

The absolute change from baseline (Day 1) values to all post-surgery visits of duplex ultrasound parameters will be summarized. Summary statistics will also be provided at each time point.

The methods and endpoints regarding the efficacy parameters employed in this study are consistent with current clinical practice and are meaningful to the research community. Every attempt has been made to minimize the variability on the part of the surgeon when using this product. The results of this study will be used to determine the sample size of subsequent clinical studies.

## 9.4. Other Analyses

All clinical parameters will be listed for all patients treated at each study visit. Descriptive statistics will be summarized for continuous outcomes such as age and BMI. If necessary, number and percentage of patients will be reported for categorical outcomes.

## 9.5. Sample Size Rationale

Up to 25 patients will be recruited into the study. As limited data evaluating the use of HAV to treat PAD are available, this Phase 2 study was designed to provide preliminary evidence of safety and efficacy.

The study is not powered to assess the efficacy of the HAV.

## 9.6. Interim analyses

There is no formal interim analysis.

# 10. STUDY MANAGEMENT AND DATA COLLECTION

## 10.1. Ethical Conduct of the Trial

This study will be conducted according to the protocol; 21 CFR Parts 11, 50, 54, 56, and 312; the World Medical Association Declaration of Helsinki (Appendix II) and Good Clinical Practice (GCP). Each investigator will conduct the trial according to applicable local or regional regulatory requirements.

## 10.2. Institutional Review Board

IRBs must be constituted according to the applicable state and federal requirements, including International Conference on Harmonization (ICH) GCP.

It is the responsibility of each investigator to submit the protocol, Investigator Brochure, subject informed consent, subject recruitment materials (if applicable), and other documentation as required by the IRB to his/her IRB 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 must be obtained from the IRBs and provided to the CRO prior to the release of clinical study supplies to the investigational site and commencement of the study. If any member of the IRB has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained.

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

## 10.3. Subject Informed Consent

Prior to any study procedures being performed, subjects and persons conducting the consent discussion will be required to sign and date the IRB-approved informed consent, and each subject will be given a copy. In addition, this information should be recorded in the subject's medical record (i.e., source document).

The written consent document will embody the elements of informed consent as described in the World Medical Association Declaration of Helsinki, 21 CFR Part 50.25, ICH E6 guideline (GCP), and in accordance with any local regulations. The investigator is responsible for the preparation, content, and IRB approval of the informed consent document. The consent form must be approved by the site's IRB and be acceptable to Humacyte.

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

## 10.4. Amendments to the Protocol

An amendment must be agreed to in writing by Humacyte and submitted to the Food and Drug Administration (FDA) and approved by IRBs 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 patient; however, approval must be obtained as soon as possible thereafter. Any agreed amendments must also be signed by the Principal Investigator.

## 10.5. Study Initiation

The investigator must not enroll any patients 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 Principal Investigator will not be supplied with IMP until all necessary pre-study requirements have been completed and essential signed documents provided to the CRO.

## 10.6. Study Monitoring

It is the responsibility of the 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 into 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.

## 10.7. Case Report Form

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

The investigator is responsible for ensuring that data are properly recorded on each patient's eCRF and related documents. An investigator who has signed the protocol signature page 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 the sponsor.

## 10.8. 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.

## 10.9. Retention of Records

All documentation pertaining to the study will be kept by Humacyte or their designee in accordance with ICH guidelines and US FDA regulations.

The investigator will maintain a study file, which should be used to file the Investigator Brochure, protocol, and IMP records; correspondence with the IRB and Humacyte; and other study-related documents.

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 drug disposition to enable evaluations or inspections from regulatory authorities and Humacyte or its designees.

The investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the IMP for the indication for

which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 5 years after the investigation is discontinued. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the sponsor. In addition, the investigator must make provision for the subject's medical records to be kept for the same period of time. No data should be destroyed without the agreement of Humacyte. Humacyte will inform the investigator in writing when the trial-related records are no longer needed. Subject's medical records and other original data will be archived in accordance with the archiving regulations or facilities of the study site.

## 10.10. Protocol Deviations

A protocol deviation is any noncompliance with the protocol or 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 the sponsor and the IRB 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 the sponsor who will agree on the necessary actions to be taken.

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

## 10.11. 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 patient accordingly.

## 10.12. Audit

It is the responsibility of CRO and Humacyte 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. The auditor and regulatory authorities will require authority from the investigator to have direct access to the subject's medical records.

# 11. REPORTING

Following completion of follow-up of all patients to the 12-month endpoint, the results will be evaluated by Humacyte or a designee for clinically meaningful findings. A clinical study report will be generated, including a summary of all available data, statistical measures, tabulated results, graphical results and interpretations. This report will be submitted to regulatory authorities in a timely manner. An addendum to the report will be generated to include data up to 60 months follow-up. This addendum will be submitted to regulatory authorities in a timely manner.

# 12. QUALITY CONTROL AND QUALITY ASSURANCE

Following written standard operating procedures, 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 the 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 the sponsor, and inspection by local and regulatory authorities.

Quality control procedures will be implemented for data entry and the generation of data quality control checks and 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 patients 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 patient's decision to participate throughout the clinical investigation,
- avoids any coercion or undue improper influence on, or inducement of, the patient to participate,
- does not waive or appear to waive the patient's legal rights,
- uses native non-technical language that is understandable to the patient,
- provides ample time for the patient to read and understand the informed consent form and to consider participation in the clinical investigation,
- provides the patient 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 the sponsor any appropriate modification(s) of the protocol

- refrain from implementing any modifications to the protocol without agreement from the sponsor, IRB, 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 the sponsor in the eCRFs and in all required reports
- maintain the clinical trial material accountability records
- allow and support the sponsor to perform monitoring and auditing activities
- be accessible to the monitor and respond to questions during monitoring visits
- allow and support regulatory authorities and the IRB when performing inspection activities
- ensure that all clinical-investigation-related records are retained as specified in this protocol.

## 13.3. Medical Care of Patients

The Principal Investigator shall:

- provide adequate medical care to a patient during and after a patient's participation in a clinical investigation in the case of AEs
- inform the patient of the nature and possible cause of any adverse events experienced
- inform the patient of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required
- provide the patient 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 patient is enrolled in a particular clinical investigation

- inform, with the patient's approval or when required by national regulations, the patient's personal physician about the patient's participation in the clinical investigation
- make all reasonable efforts to ascertain the reason(s) for a patient's premature withdrawal from the clinical investigation while fully respecting the patient's rights.

## 13.4. Safety Reporting

The Principal Investigator shall:

- record every adverse event together with an assessment, in accordance with Sections 8 and 9 of this protocol,
- report to the sponsor, without unjustified delay, all serious adverse events and medically significant events as specified in Sections 8 and 9 of this protocol,
- supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting of a particular event.

# 14. SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

The sponsor may suspend or prematurely terminate either a clinical investigation in an individual investigation site or the entire clinical investigation for significant and documented reasons.

A Principal Investigator, IRB, 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 patients arises during the clinical investigation, or when so instructed by the IRB or regulatory authorities, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk is confirmed.

The sponsor shall consider terminating or suspending the participation of a particular investigation site or investigator in the clinical investigation 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, the sponsor suspends or prematurely terminates the investigation at an individual investigation site, the sponsor shall inform the responsible regulatory authority if required and ensure that the IRB is notified. If the suspension or premature termination was in the interest of safety, the sponsor shall inform all other Principal Investigators.

If suspension or premature termination occurs,

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

2. the Principal Investigator or authorized designee shall promptly inform the enrolled patients 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

A Publication Committee comprising the Principal Investigator from each participating site and a representative of Humacyte will oversee all publication of data from this study. Prior to submitting for publication, presenting, using for instructional purposes, or otherwise disclosing the results of the study, the investigator agrees to allow the Publication Committee and Humacyte a period of at least 30 days (or, for abstracts, at least 5 calendar days) to review the proposed publication or disclosure prior to its submission for publication or other disclosure. Publications or disclosures of study results shall not include other confidential information belonging to Humacyte. 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, at the investigator's option, a sufficient time to allow Humacyte to seek patent protection of the invention. For multicenter studies, the first publication or disclosure shall be a complete, joint multicenter publication or disclosure. This statement does not give Humacyte any editorial rights over the content of a publication or disclosure, other than to restrict the disclosure of Humacyte's confidential information. If a written contract for the conduct of the study is executed which includes publication provisions inconsistent with this statement, then that contract's publication provisions shall apply rather than this statement.

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# APPENDIX 1. HAV CLINICAL VISIT SCHEDULE

| | **Screening** (Days -35 to -1) | **D 1** | **D 5** | **D 29** +/- 4 days | **M 3** +/- 14 days | **M 6** +/- 14 days | **M 9** +/- 14 days | **M12 /ET[2]** +/- 14 days | **M18-M60 /ET[2]** +/- 30 days |
|---|---|---|---|---|---|---|---|---|---|
| Informed consent | X | | | | | | | | |
| Medical & smoking histories; review of PAD therapy | X | X | | | | | | | |
| Review of medications | X | X | X | X | X | X | X | X | |
| Physical exam including ischemic lesions on implant leg | X | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X | X[1] |
| ECG (12-lead) | X | | | | | | | | |
| Review prestudy angiography/CT angio & vein mapping | X | | | | | | | | |
| Vital signs | X | X | X | X | X | X | X | X | |
| Eligibility (inclusion/exclusion criteria) | X | X | | | | | | | |
| HAV implantation and angiography/intraop ultrasound | | X | | | | | | | |
| Documentation of surgery and any complications | | X | | | | | | | |
| Clinical chemistry; hematology; coagulation | X | | | | | X | | | |
| HbA1c | X | | | | | | | | |
| Urine or serum pregnancy test (WOCBP) | X | | | | | | | | |
| PRA | X | | | | | X | | | |
| Clinical duplex ultrasound | | | | X | X | X | X | X | X[5] |
| High resolution duplex ultrasound | | X[3] | | | X | X | | X | |
| Endothelium-dependent, flow-mediated vasodilatation [4] | | | | X | | | | X | |
| CT angiography | | | | X | | X | | X | X[6] |
| AEs | | X | X | X | X | X | X | X | X[7] |

| | **Screening** (Days -35 to -1) | **D 1** | **D 5** | **D 29** +/- 4 days | **M 3** +/- 14 days | **M 6** +/- 14 days | **M 9** +/- 14 days | **M12 /ET[2]** +/- 14 days | **M18-M60 /ET[2]** +/- 30 days |
|---|---|---|---|---|---|---|---|---|---|
| Documentation of HAV interventions | | X | X | X | X | X | X | X | X |
| PAD symptoms assessment (VascuQol) | X | | | X | X | X | X | X | X |
| ABI – supine after 5 minute rest | X | | | X | X | X | X | X | X |
| 6 minute walk test | X | | | | X | | | X | |
| Patient Survival | | | | | | | | | X |

Abbreviations: AEs, adverse events; D, day; ECG, electrocardiogram; ET, early termination; HAV, human acellular vessel; M, month; PRA, panel reactive antibody.

NOTE: Visits should be performed using the following time windows: Screening, Day -35 to -1; Day 5 (or prior to hospital discharge, if earlier); Day 29, ± 4 days; Months 3,6,9,12, ± 14 days

1 Physical examination includes focused vascular clinical exam of HAV site (incl. patency assessment) and physical exam for lymphadenopathy (at D5 and D29) and to evaluate AEs.
2 Patients withdrawn before Month 12 should complete an ET visit that correlates with the procedures at Month 12. Patients withdrawn after Month 12 and prior to Month 60 should complete an ET visit that correlates with procedures post Month 12 through Month 60.
3 Intraoperative
4 Duplex ultrasound assessment of endothelium-dependent flow-mediated vasodilatation testing in a subset of patients
5 Clinical duplex ultrasound not required on Month 60
6 CT angiography only performed on Month 60. This is not required as part of an ET visit
7 Collection of SAEs and Events of Special Interest through Month 60

**If, at any of the scheduled visits through Month 12, duplex ultrasound surveillance suggests the development of a ≥ 50% stenosis within the HAV but immediate intervention is not required closer follow up should be considered. Intervention to manage any such stenosis is at the discretion of the investigator taking into account the degree and rate of progression of the stenosis.**