A Phase 2/3 Study for the Evaluation of Safety and Efficacy of Humacyte's Human Acellular Vessel for Vascular Replacement or Reconstruction in Patients with Life or Limb-threatening Vascular Trauma

Study No.: CLN-PRO-V005

Investigational Product: Human Acellular Vessel (HAV)

Study No.: CLN-PRO-V005

IND No.: 15263

Version Date: 24May2023

Version: 4.0

Sponsor: Humacyte Global, Inc.
2525 East NC Highway 54
Durham, NC 27713

Sponsor Approval:

Shamik Parikh Digitally signed by Shamik Parikh
Date: 2023.05.24 17:11:31 -04'00'

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Confidentiality Statement

REVISION HISTORY

Protocol Version	Active Region(s)	Date Finalized
Original Protocol	USA	29 December 2015
Version 2.0	USA	24 October 2016
Version 3.0	USA, Israel	18 July 2018
Version 3.1	For potential Poland sites – not implemented.	22 June 2021
Version 3.2	USA	18 August 2021
Version 3.3	USA (added pediatric enrollment)	12 August 2022
Version 4.0	USA (Master protocol) **Rationale for key revisions:** - Incorporate modifications requested by the Agency during the March 2022 meeting (March 30, 2022 (Reference IND 16746 CRMTS #13939 Meeting Summary March 30, 2022 Type B OIND Teleconference) and during the March 2023 Type C pre-BLA meeting (reference): o Separate analyses for the group of patients with non-iatrogenic arterial trauma of the extremities, and the rest of the patients enrolled (patients with iatrogenic and torso injuries). o Inclusion of pediatric patients and clarification of category of eligible pediatric patients o Modification of statistical analysis section to include While-on-Treatment analysis methodology and define the estimands. - Serious Adverse Event definition updated to align with industry standards and FDA guidance	24 May 2023

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

STUDY SITE PRINCIPAL INVESTIGATOR AGREEMENT

Protocol Title: **A Phase 2/3 Study for the Evaluation of Safety and Efficacy of Humacyte's Human Acellular Vessel for Vascular Replacement or Reconstruction in Patients with Life or Limb-threatening Vascular Trauma**

Study No.: CLN-PRO-V005

Version: 4.0

I agree:

- To assume responsibility for the proper conduct of the study at this site, and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by Humacyte Global, Inc. (Humacyte) or its authorized representatives.
- Not to implement any deviations from or changes to the protocol (including protocol amendments) without agreement from Humacyte and prior review and written approval from the Institutional Review Board (IRB) and relevant regulatory authorities, 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 product, as described in this protocol and any other information provided by Humacyte including, but not limited to, the current Investigator Brochure (IB) or equivalent document.
- To ensure that all persons assisting me with the study are adequately informed about the investigational product and trained on all study-related duties and functions.
- That I have been informed that certain regulatory authorities require Humacyte to obtain and supply details about the investigator's ownership interest in Humacyte or the investigational product (IP), and more generally about his/her financial ties with Humacyte.
- That I have been informed that Humacyte will use and disclose the information solely for the purpose of complying with regulatory requirements.

Principal Investigator: _____ _____

Signature Date

Printed Name and Title: _____

Institution Name: _____

Institution Address: _____

_____

PROTOCOL SYNOPSIS

Title of Study:	A Phase 2/3 Study for the Evaluation of Safety and Efficacy of Humacyte's Human Acellular Vessel for Vascular Replacement or Reconstruction in Patients with Life or Limb-threatening Vascular Trauma
Protocol Number:	CLN-PRO-V005
Study Phase:	Phase 2
Name of Sponsor/Company:	Humacyte Global, Inc.
Planned Study Sites:	Up to 35 sites in the United States (US), Israel, and Ukraine will be recruited to enroll patient.
Planned Sample Size:	Up to 100 patients
Study Population:	Patient with vascular trauma to size appropriate vessels in the limb or torso, requiring replacement or reconstruction.
Inclusion Criteria:	1. Patient with life or limb threatening traumatic injury to an arterial vessel in the limb or torso, other than the heart, which requires replacement or reconstruction. 2. Preoperative imaging or clinical examination indicates the damaged vessel has a defect length of ≤ 38cm and is appropriately size matched to the 6mm Human Acellular Vessel (HAV) per the judgment of the treating surgeon taking into account vasoconstriction and situational inflow and outflow considerations. 3. Autologous vein graft is either not feasible in the judgment of the treating surgeon (e.g., because of lack of availability of suitable conduit, presence of severe venous insufficiency) or is not desirable because of the urgency of revascularization. 4. Adults aged 18 to 85 inclusive (all sites) and adolescents who have achieved Tanner Sexual Maturity Rating Stage V (US sites Only). 5. Able to communicate meaningfully with investigative staff and able to comply with study procedures. If the patient is unconscious, then information from a reliable witness indicates that the patient would normally be able to understand and comply with study procedures. 6. Patient or legal representative is able, willing and competent to give informed consent. 7. Life expectancy of at least 1 year.
Exclusion Criteria	1. Mangled Extremity Severity Score (MESS) of ≥ 7. 2. Limb at high risk of amputation despite vascular reconstruction (e.g., because of crush injury). 3. Catastrophic injuries that make survival unlikely (e.g., Abbreviated Injury Scale (AIS) > 5 or Injury Severity Score (ISS) >60). 4. HAV may not be used for coronary artery repair. 5. Women known to be pregnant. 6. Known medical condition which would preclude long term antiplatelet therapy after resolution of acute injuries. 7. 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).

<table>
<tr><td></td><td>8. Previous exposure to HAV.
9. Known participation in any investigational study within the last 30 days.
10. Employees of the sponsor or patients who are employees or relatives of the investigator.</td></tr>
<tr><td>Expected Enrollment Start</td><td>3Q2018</td></tr>
<tr><td>Accrual Period:</td><td>Enrollment will close on or before December 31, 2024.</td></tr>
<tr><td>Study Duration</td><td>The active study duration for each study participant will be 36 months from HAV implantation. All patients will be followed for the initial 12 months. Beyond 12 months (Long-Term Follow Up), only patients with a patent HAV will be followed out to a total of 36 months from HAV implantation. The total expected duration of the clinical study is 61 months.</td></tr>
<tr><td>Study Design</td><td>Prospective, multicenter, non-randomized study</td></tr>
<tr><td>Investigational Medicinal Product/Intervention Description</td><td>Patients will be implanted with a Humacyte Human Acellular Vessel (HAV) as an interposition replacement or bypass using standard vascular surgical techniques.</td></tr>
<tr><td>Primary Objectives and Endpoints</td><td>
<table>
<tr><th colspan="2">Primary Safety</th></tr>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>To determine infection rates of the HAV</td><td>HAV Infection</td></tr>
<tr><td>To evaluate the safety and tolerability of the Humacyte HAV in vascular trauma patients following surgery for vascular replacement or reconstruction due to life- or limb-threatening trauma of the extremities</td><td>Adverse Events</td></tr>
<tr><th colspan="2">Primary Efficacy</th></tr>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>To determine the primary patency of the HAV at 30 days in vascular trauma patients following surgery for vascular replacement or reconstruction due to life- or limb-threatening trauma of the extremities</td><td>Primary HAV patency for at least 30 days after implantation</td></tr>
</table>
</td></tr>
</table>

Secondary Safety Objectives and Endpoints

Key Secondary Safety	
Objectives	**Endpoints**
To determine mechanical stability of the HAV based on freedom from aneurysmal degeneration, anastomotic bleeding or spontaneous rupture, infection, or significant stenosis.	Adverse events of special interest HAV infection
To determine the durability of the HAV repair in terms of freedom from interventions needed to maintain or restore HAV patency.	Adverse events HAV interventions
To determine amputation rate	Amputations
To determine mortality	Death
To determine the rate of HAV removal	Partial or complete removal of HAV
To determine the rate of post-operative surgical site infection	Post-operative surgical site infection

Secondary Efficacy Objectives and Endpoints

Key Secondary Efficacy	
Objectives	**Endpoints**
To determine the patency of the HAV at least 30 days, regardless of interventions	Patency (Secondary) for at least 30 days after implant
To determine the ability of the HAV to remain infection free for 30 days	Conduit infection in 30 days after implant
To determine the rate of limb salvage for 30 days	Amputation in 30 days after implant
Secondary Efficacy	
To determine the long-term limb salvage	Amputation
To determine the long-term patency of the HAV, regardless of interventions	Patency (Secondary)
To determine the long-term ability of HAV to stay infection free	HAV infection
To determine the rates of interventions needed to maintain/restore patency in the HAV	HAV interventions to maintain/restore patency
To determine patient survival	Death
To evaluate remodeling of the HAV	Histopathology of any clinical explants

Protocol Approval	Version 4.0 Approved 24May2023

Figure 1 Study Schematic

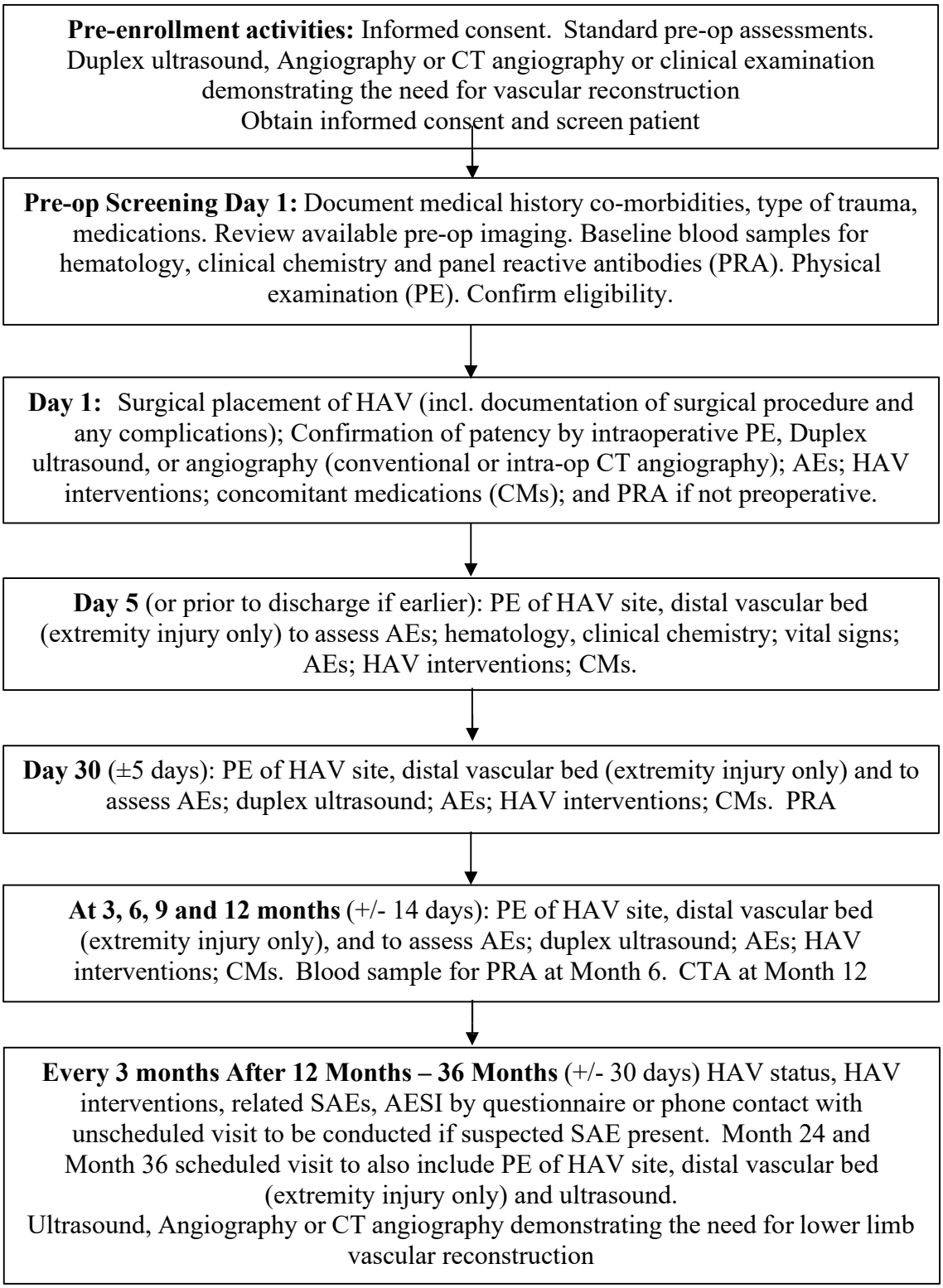

Table 1 Schedule of Visits and Assessments

	Pre-op screening D1	D 1	D 5 or prior to d/c	D 30 ± 5 days	M3 ± 14 days	M 6 ± 14 days	M 9 ± 14 days	M12/ET† ± 14 days	M15-M36 †± 30 days
Informed consent	X								
Medical history and nature of trauma	X								
Concomitant medication	X	X	X	X	X	X	X	X	
Physical exam [1]	X	X	X	X	X	X	X	X	X [7]
Pre-op Ultrasound or CT angiography [2]	X								
Vital signs			X						
Eligibility (inclusion/exclusion criteria)	X								
HAV implantation and intraoperative confirmation of patency [3]		X							
Documentation of surgery and any complications		X							
Clinical chemistry	X [5]		X						
Hematology	X [5]		X						
PRA	X [5]			X		X		X [6]	
Duplex Ultrasound [4]				X	X	X	X	X	X [7]
CT angiography								X	
AEs		X	X	X	X	X	X	X	X [8]
Documentation of HAV interventions		X	X	X	X	X	X	X	X[8]

Abbreviations: AEs, adverse events; D, day; d/c, discharge; ET, early termination; HAV, human acellular vessel; M, month; PRA = panel reactive antibodies PRA = panel reactive antibodies.

1. Physical examination includes clinical exam of the operative limb and HAV at all post-operative visits (incl. patency assessment on D1) and physical exam to evaluate AEs; include distal vascular bed (extremity injury only)

2. Pre-op imaging is at the discretion of the investigator based on the clinical condition of the patient. It may be omitted if not deemed necessary in order to proceed to vascular surgical repair.
3. Determination of intraoperative HAV patency can be done by physical exam, Doppler, angiography or ultrasound at the discretion of the investigator.
4. An alternative imaging method (CTA, MRI, etc.) may be substituted for duplex ultrasound at the discretion of the investigator if it is medically appropriate and in the best interest of the patient.
5. Measured at preoperative screening when possible; if PRA titer not obtained preoperatively, it must be completed within 12 hours after HAV implantation.
6. PRA only collected at ET visit if the visit occurs before Month 6 collection.
7. Visits at month 24 and month 36 to be conducted in person with physical exam of the HAV site and duplex ultrasound imaging of HAV.
8. The status of the patient and HAV will be ascertained every 3 months post Month 12 until 36 months after HAV implantation by telephone contact with the patient and/or his physician. Only related SAEs and all AESI will be reported after 12 months. If a suspected SAE related to HAV is discovered an unscheduled visit should be conducted to investigate.

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HAV	Human acellular vessel
HIV	Human immunodeficiency virus
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IM	Intramuscular
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization
IU	International unit
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
M	Month
NYHA	New York Heart Association
OTC	Over-the-counter
PAD	Peripheral arterial disease
PE	Physical examination
PHI	Protected health information
PI	Principal Investigator
PRA	Panel reactive antibodies
PT	Prothrombin time
PTFE	Polytetrafluoroethylene
QA	Quality Assurance

Abbreviation	Definition
QC	Quality Control
RRT	Renal replacement therapy
SAE	Serious adverse event
SFA	Superficial Femoral Artery
SOP	Standard operating procedure
SVS WIfI	Society for Vascular Surgery: Wound, Ischemia, and foot Infection
US	Ultrasound
USA	United States of America
WFI	Water for injection
WBC	White blood cell(s)
WHO	World Health Organization

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).

Key Study Management Personnel

CRO Safety Representative:

Todd Fisher
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2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1. Background Information

In the civilian population, traumatic vascular injuries are mainly concentrated to the limbs and torso (abdomen, retroperitoneum, thorax and thoracic outlet). According to the PROspective Observational Vascular Injury Treatment (PROOVIT) database, designed to collect vascular trauma injuries from 24 Level I and Level II trauma centers in the United States, vascular injuries in the lower limb, torso, upper limb and neck have a distribution of 41%, 30%, 22%, and 6%, respectively (Dubose, 2015; Faulconer, 2018). These reports incorporate a significant percentage of relevant venous injuries in addition to arterial. Additionally, in the civilian population, lower extremity bone fractures with associated arterial injuries are common, due to motor vehicle accidents, gunshot wounds, dog bites, and other situations resulting in blunt or penetrating trauma (Akingba, A. George, 2012; Akingba, A. G., 2013; Andrikopoulos, 1995; Helfet, 1990). In fact, the incidence of this type of vascular injury has increased considerably in the past 50 years (Andrikopoulos, 1995). Although this type of injury represents less than 1% of all civilian injuries, fractures with associated vascular damage require special attention because of their potentially severe complications, including limb necrosis and amputation.

Currently, in order to attempt to salvage the injured limb or end-organ in the distal vascular bed and to prevent life threatening hemorrhage the vascular component of these injuries is treated with interposition or bypass grafting. This type of reconstruction is performed by using either autologous vein from the patient (typically great saphenous vein), or by using a synthetic graft, such as ePTFE or Dacron. However, the use of these grafts in the civilian population is not always possible or without additional risks. The patient may not have adequate autologous vein for harvest, and in many of these cases, such as dog bite injuries, the wound is “dirty” and a synthetic vascular substitute is contraindicated due to the risk of infection (Akingba, A. George, 2012; Akingba, A. G., 2013). Thus, civilians would benefit from a vascular graft that does not contain infection-prone synthetic material and has similar properties as human tissue but does not require time consuming or high morbidity procedures to harvest vessels from the patient.

Military personnel could also benefit from an off-the-shelf biologic vascular graft. In modern combat, the incidence of vascular injury is much greater than in previous wars. The rate of vascular injury in the Vietnam War was 2-3%. But between 2002-2009, the rate of vascular injury was over 12% in a study of over 13,000 battlefield injuries. In combat scenarios vascular injuries occur in all locations of the body, but injuries to the lower extremities are the most common, followed by vascular injuries to the upper extremity, and then neck, followed by torso. (Rasmussen, 2018). Improvised Explosive Devices, or IED’s, caused more than 3,000 casualties per year during recent conflicts (Cordesman and Greenough, 2010; Cordesman and Lemieux, 2010). Arterial damage, laceration and thrombosis can require vascular reconstruction to save tissues from ischemia, necrosis, and further amputation. Harvesting autologous vein for vascular reconstruction is problematic because IED casualties often have multi-limb injuries, making harvest of autologous vein highly risky or impossible (Holcomb, 2010). Synthetic vascular reconstruction using synthetic vascular grafts made from Teflon (ePTFE)/Dacron is relatively

contraindicated, since IED wounds are always "dirty", and bacteria in the wound can colonize the synthetic graft, causing abscesses and sepsis.

Thus, there is a significant unmet medical need for alternative grafts, which can be used in situations where autologous vein is unavailable or undesirable to use and which more closely mimic human vascular tissue to avoid or reduce the infection complications associated with ePTFE and Dacron.

2.2. Scientific Rationale

Humacyte has developed an acellular, human tissue engineered vascular conduit, the human acellular vessel (HAV, to provide an alternative to synthetic materials and to autologous grafts in the repair of traumatic vascular damage. Because this product mimics native vascular tissue, it may possess the advantages of an autologous graft; it also has the benefits of synthetic grafts in that it is available off-the-shelf. 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 vessels available. In addition, the HAV may not exhibit 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 (Dahl, 2011; Prichard, 2011; Quint, 2011). Upon implantation, the collagen matrix comprising the HAV is infiltrated with host cells and remodeled by the host. This could result in a vascular structure more similar to the histological composition of the native vascular tissue; this remodeling may improve bypass longevity and make the HAV less likely to become infected. The latter potential advantage is of critical importance in the repair of peripheral vascular trauma where most wounds are heavily contaminated.

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 both acutely and chronically,
- functional aspects of product implanted into animal models as an arteriovenous conduit, and
- 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 material was nontoxic, well-tolerated, and met standards for biocompatibility. Generally, the HAVs functioned as intended and maintained patency during the implantation period. See the HAV Investigator Brochure for a detailed summary of nonclinical data.

Prior to implantation, the HAV has mechanical properties (burst pressure and suture retention strength) comparable with native human arteries and veins (Table 2) There were no observations indicative of deterioration of HAV strength after long-term implantation into baboons.

Table 2 Summary of Mechanical Properties of Explanted Acellular Vessels

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]

a From L'Heureux et al, Nature Medicine, 2006. (L'heureux, 2006)

In the chronic animal studies, Humacyte vessels equivalent to the HAV but produced using canine cells were implanted into 12 dogs (canine acellular vascular graft, CAVG) in a variety of anatomical locations. The human HAV was similarly implanted into 14 baboons. 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 ePTFE 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, or necropsy data. The HAVs could be accessed by venipuncture and hemostasis was achieved after needle puncture.

Under 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 $CD68^+$ macrophages in the venous intimal tissue. Studies have shown a substantial macrophage population has been observed within venous intimal tissue adjacent to inflammatory ePTFE arteriovenous grafts (Kelly, 2002; Roy-Chaudhury, 2001). Only sparse $CD68^+$ 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 ePTFE grafts (Prichard, 2011).

Over time, the organization and composition of extracellular matrix (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 vs 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.

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

2.4. Summary of HAV Clinical Studies

Human studies are ongoing in the United States (US), Europe, and Israel. In all, eight clinical studies were initiated to evaluate three clinical indications for use of the HAV. Seven studies completed their planned follow-up times with three continuing to follow patients long-term (CLN-PRO-V001, CLN-PRO-V002, CLN-PRO-V004, and CLN-PRO-V007). One clinical study NCT03005418 (EudraCT #2020-003383-12) or CLN-PRO-V005 (i.e., V005) that is evaluating HAV for repair of vascular trauma is continuing to enroll patients. As of 10 April 2022, a total of 374 patients with ESRD, 35 patients with PAD, and 51 patients with vascular trauma have had the HAV implanted. In addition, an HAV has been implanted in over 30 cases under an Expanded Access program. The first implant for hemodialysis was performed in December 2012, the first for peripheral arterial bypass in October 2013, and the first implant for trauma in September 2018. Across all clinical studies the total treatment exposure to HAV is approximately 1,005 patient-years, with approximately 830 patient-years, 119 patient-years, and 56 patient-years in ESRD, PAD, and vascular trauma patients, respectively.

More information on the clinical profile of the HAV in these ongoing studies is provided in the Investigators Brochure.

2.4.1. Experience in Patients Undergoing Peripheral Arterial Bypass

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 peripheral arterial disease. Pre-operative imaging (conventional or 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 (conventional or intra-op CT angiography) or ultrasound. The patient was then followed up at study visits at 15 days, 6 weeks and 3, 6, 12, 18 and 24 months. At each visit safety was assessed by clinical examination and adverse events, and the HAV was examined using duplex ultrasound to visualize the entire length to confirm patency, flow and to detect stenosis, aneurysm development or dilatation.

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

Secondary objectives include assessment of the 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 and long-term follow-up is currently ongoing.

CLN-PRO-V002 Study Results (72 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 HAV or implantation procedure.

Kaplan-Meier (K-M) 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 patients). Those 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.

At six years (72 months), six patients have completed follow-up, with five of six patients retaining HAV patency (i.e., primary patency = 4 and secondary patency = 1), which was confirmed by Doppler ultrasound. Three of the long-term patients died during follow-up; one from cancer at 71 months and two from other non-HAV-related causes at 54 months and approximately 67 months post-implant (Gutowski, 2023). Also, one patient voluntarily withdrew from the study at 61 months post-implant. During long-term follow-up (i.e., post 24 months), one patient had two thrombectomies performed. For all remaining patients, no interventions and no infections were documented. Overall, 7 deaths were recorded at the 72-month endpoint, for a

mortality rate of 35% in this patient cohort (i.e., severe PAD with 7-year follow-up). No deaths were attributable to the HAV.

In conclusions, this study demonstrated that

- Humacyte HAV was safe and well tolerated in patients with PAD.
- 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.
- The HAV was not immunogenic.

2.4.2. Experience in Patients Undergoing Hemodialysis

Two phase 2 trials, one in Poland (CLN-PRO-V001) and one in the US (CLN-PRO-V003) have completed enrollment. Both recruited patients requiring hemodialysis access for end-stage renal disease who were not suitable for creation of an AVF. Most patients 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 panel of reactive antibodies (PRA) response, development of IgG antibodies to the extracellular matrix material in the HAV, the evaluation of patency 2 years after implantation, and an assessment of the need for interventions to maintain or restore patency. Follow-up has now been extended up to 120 months.

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

CLN-PRO-V001 and CLN-PRO-V003 Study Results

All patients (n=60) have now completed at least 24 months since implantation (or had a censoring event). The first patients 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 graft aneurysm was reported in Study CLN PRO V001 (moderate in intensity, considered possibly related to the HAV and considered not related

to the implantation 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 patients had elevations in their PRA levels: all 3 patients had experienced one or more renal transplant failures; one patient recently; one patient developed septic shock about a month before the elevated value; and the third patient, who was severely debilitated with a decubitus ulcer, died approximately a month after HAV abandonment.

IgG titers increased in 5 patients; 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 patient who maintained primary patency.

Adverse events (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 K-M survival analysis (Lawson, 2016). Based on these K-M plots the patency at 6, 12 and 24 months is estimated to be 60%, 26% and 15% (primary patency) and 97%, 91% and 77% (secondary patency).

2.5. Human Acellular Vessel Host Response and Remodeling Data

Humacyte has been able to assess the general host response to the HAV in 8 human participants; this was accomplished through the microscopic examination of explanted HAV and adjoining tissue samples that were obtained during surgical revision procedures (Kirkton, 2018; Kirkton, 2019; Lawson, 2016). 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 neosynthesis and reorganization of ECM components representative of those typically occurring in native blood vessels.

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

In humans, 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, vascular organization, and structure; namely, cells 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-constricting fibrous tissue formed around the HAV implant. 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 neosynthesis 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 mature, organized pattern, with distinct fibers and a prominent circumferential alignment evident in explanted samples compared to 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 2). 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.

Based on this evidence, the HAVs were remodeled by the host after implantation to form a vascular-like structure 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 neosynthesis and reorganization of ECM components of a type that typically occurs in native blood vessels were observed in the explanted HAV. The cellular infiltration and ECM remodeling patterns were indicative of the integration of the HAV into the host physiology.

Figure 2 Images of Mid-Vessel Segment Explanted at 11 Months After HAV Implantation

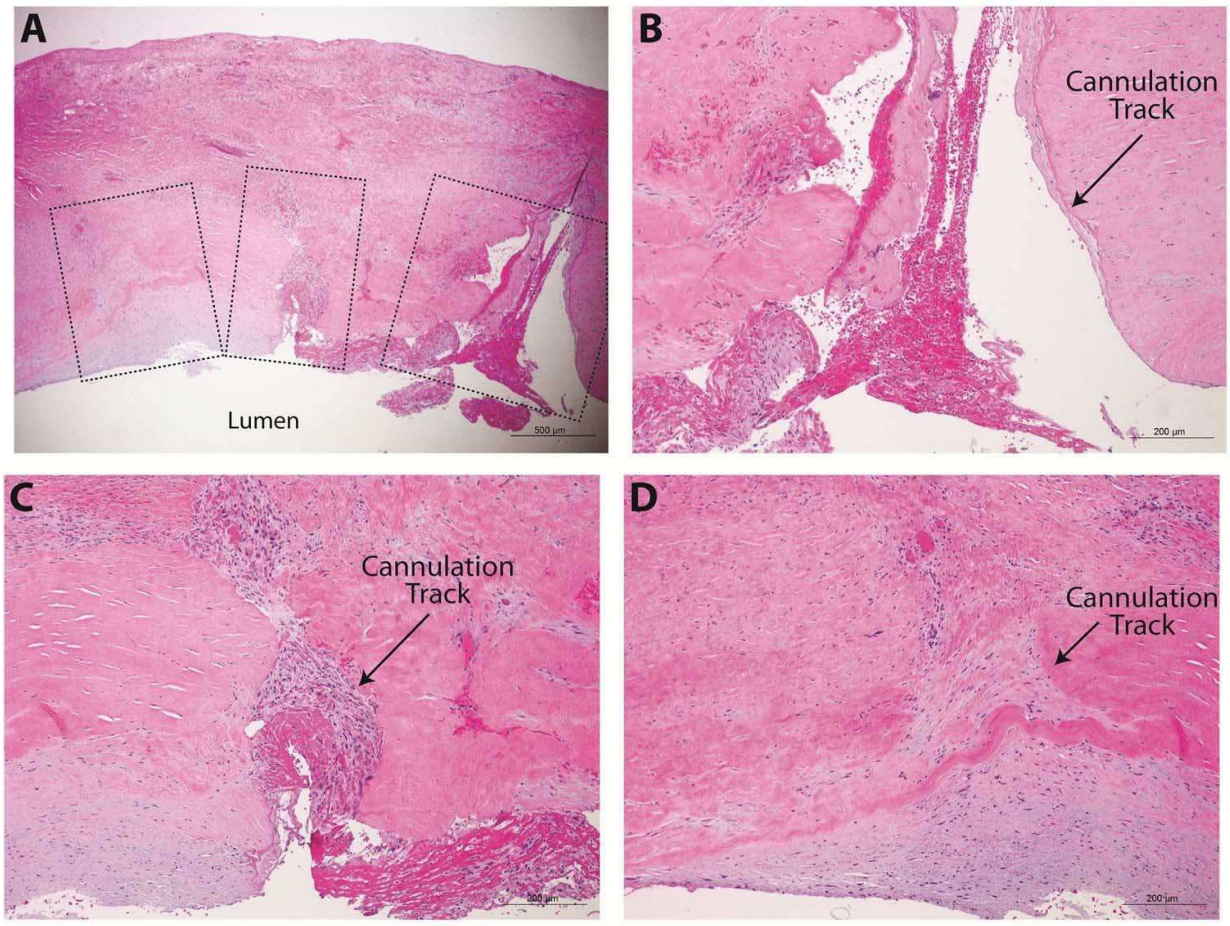

Figure 2. Histopathology images of mid-vessel HAV segment explanted 11 months after HAV implantation. Panel A: Low magnification showing 3 cannulation sites (in dashed boxes) with several prior cannulation tracts from dialysis access; Panel B: Fresh cannulation track with a fresh clot extending into the tract from the lumen; Panel C: Cannulation track during remodeling; and Panel D: shows an older cannulation track that has been repaired. Panels C and D both 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 (Kirkton, 2019; Lawson, 2016).

Conclusions

Clinical experience indicates that the HAV remains mechanically strong over implantation periods of more than 60 months with no evidence of dilatation. During more than 200 patient-years of follow up across the three phase 2 studies only one case of infection of the HAV material itself has been reported. The serious adverse event (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.

2.6. Potential Risks and Benefits

This is a first-in-human study in which the HAV will be used to repair vascular injuries within the torso (thorax, thoracic outlet, abdomen, and retroperitoneum) as well as the extremities (upper and lower limbs).

Risks associated with HAV use in vascular repair specific to these locations have not been specifically characterized. However, these risks are not expected to be significantly different than those experienced/reported when used in the upper or lower extremity for AV access or arterial reconstruction.

The Data Monitoring Committee (DMC) will review safety data of the torso injuries on the earlier of when the first torso patient reaches 3 months post-implantation or when the first 2 torso patients have both reached 30 days post-implantation. Overall recruitment will be restricted to a maximum of 100 patients who receive implants.

This is also the first time the HAV will be used to repair vascular injuries in a pediatric population. Because enrollment in this study is limited to older adolescents, who have reached pubertal development Tanner Stage V, these risks are not expected to be significantly different than those experienced/reported in adults.

2.6.1. Potential Risks

It is anticipated that patients 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 systemically
- Stenosis of the conduit or its anastomoses
- Aneurysm or pseudoaneurysm formation
- Swelling of the limb
- Failure/injury to the target end-organ
- Bleeding/hemorrhage in the peritoneum or retroperitoneum

The HAV is grown using donor human aortic smooth muscle cells; the vessel is decellularized during manufacturing and thus consists of human extracellular matrix 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

determining and analyzing concentrations of panel-reactive antibodies (PRA) at various times during the study.

2.6.2. Potential Benefits

Patients who undergo implantation of the Humacyte HAV may benefit from improved patency and a reduced number of interventions versus a conventional ePTFE or Dacron graft.

- This may result from a decreased propensity for anastomotic and downstream neointimal hyperplasia, which often leads to graft occlusion with synthetic grafts.
- In addition, risks of infection 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.

Patients may also benefit from reduced morbidity secondary to harvest of autologous vessels for vascular reconstruction. Harvest of autologous vascular conduit requires additional time to perform and in the urgent/emergent trauma scenario, time is of the essence and is key to positive patient outcomes. Use of saphenous, or other autologous vessels for purposes of vascular repair in young, otherwise healthy patients prevents its future potential use for other indications (e.g., coronary bypass, etc.) in the future.

Vascular reconstruction using synthetic vascular grafts (ePTFE, or woven materials like Dacron) may be contraindicated for use in trauma cases, as the wounds are often contaminated and allow bacteria in the wound to colonize the synthetic graft. Such colonization may potentially lead to abscesses, hemorrhage secondary to anastomotic blow out, blood stream infection, and sepsis. Unlike other readily available synthetic vascular grafts made from ePTFE or Dacron, HAVs are comprised of human proteins, resulting in grafts that may be less prone to infection than synthetic materials, as shown in preclinical studies (Kirkton, 2018).

2.6.3. Risk-Benefit Rationale

The risks anticipated in this study are similar to those associated with currently marketed prosthetic grafts used for vascular repair. The potential advantages of the HAV compared to currently marketed grafts may lead to a lower complication rate and reduced need for surgical intervention and graft replacement as well as the potential for reduced secondary complications associated with autologous vessel harvest.

This is the first in man study in which the HAV will be used to repair vascular injuries within the torso (thorax, thoracic outlet, abdomen, and retroperitoneum) and so risks related to those locations have not been specifically characterized. However, these risks are not expected to be significantly different than those experienced or reported when used in the upper or lower extremity for AV access or arterial reconstruction.

This is the first in man study in which the HAV will be used to repair vascular injuries in a pediatric population. Because enrollment in this study is limited to older adolescents who have reached pubertal development Tanner Stage 5, these risks are not expected to be significantly different than those experienced/reported in adults.

3. STUDY OBJECTIVES

3.1. Primary Objectives and Endpoints

The primary objectives and the corresponding endpoints of this study are provided in Table 3.

Table 3 Primary Objectives and Endpoints

Primary Safety	
Objectives	**Endpoints**
To determine infection rates of the HAV	HAV Infection
To evaluate the safety and tolerability of the Humacyte HAV in vascular trauma patients following surgery for vascular replacement or reconstruction due to life- or limb-threatening trauma of the extremities	Adverse Events
Primary Efficacy	
Objectives	**Endpoints**
To determine the primary patency of the HAV at 30 days in vascular trauma patients following surgery for vascular replacement or reconstruction due to life- or limb-threatening trauma of the extremities	Primary HAV patency for at least 30 days after implantation

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3.2. Secondary Objectives and Endpoints

The secondary objectives for Safety and the corresponding endpoints of this study are provided in Table 4.

Table 4 Secondary Safety Objectives and Endpoints

Secondary Safety	
Objectives	**Endpoints**
To determine mechanical stability of the HAV based on freedom from aneurysmal degeneration, anastomotic bleeding or spontaneous rupture, infection, or significant stenosis	Adverse events of special interest HAV infection
To determine the durability of the HAV repair in terms of freedom from interventions needed to maintain or restore HAV patency	Adverse events HAV interventions
To determine amputation rate	Amputation

To determine mortality	Death
To determine the rate of HAV removal	Partial or complete removal of HAV
To determine the rate of post-operative surgical site infection	Post-operative surgical site infection

The secondary objectives for Efficacy and the corresponding endpoints of this study are provided in Table 5.

Table 5 Secondary Efficacy Objectives and Endpoints

Key Secondary Efficacy	
Objectives	**Endpoints**
To determine the patency of the HAV at least 30 days, regardless of interventions	Patency (Secondary) for at least 30 days after implant
To determine the ability of the HAV to remain infection free for 30 days	Conduit infection in 30 days after implant
To determine the rate of limb salvage for 30 days	Amputation in 30 days after implant
Secondary Efficacy	
To determine the long-term limb salvage	Amputation
To determine the long-term patency of the HAV, regardless of interventions	Patency (Secondary
To determine the long-term ability of HAV to stay infection free	HAV infection
To determine the rates of interventions needed to maintain/restore patency in the HAV	HAV interventions to maintain/restore patency
To determine patient survival	Death
To evaluate remodeling of the HAV	Histopathology of any clinical explants

4. STUDY DESIGN

4.1. Description of the Study Design

This is a prospective, open-label, non-randomized, multicenter Phase 2/3 study. No formal hypothesis testing is planned.

Injuries to both the limbs and torso have been permitted in the study. Moving forward after approval of this version, patients with extremity injuries will be the main target for enrollment.

Vessels of the heart are excluded. Examples of size-appropriate vessels include (but are not limited to):

- Axillary
- Brachial
- Basilic
- Popliteal
- Femoral
- Subclavian
- Brachiocephalic/innominate
- Celiac
- Hepatic
- Splenic
- Superior mesenteric
- Renal
- Iliac

4.2. Overall Structure of the Study

A schematic illustrating the overall study structure as well as the sequence and timing of planned assessments is provided in Figure 1; the corresponding schedule of assessments is provided in Table 1.

4.3. Study Endpoints

Endpoints will be assessed for up to 36 months after HAV implantation. The primary analysis of the study will be conducted when the earlier of these two milestones are reached:

a) when the last patient enrolled reaches 30 days after implantation, or

b) all patients enrolled in the initial 24-month accrual period have reached 30 days after HAV implantation.

The objectives, endpoints and the corresponding estimands for this study have been updated for this version of the protocol as described in the corresponding Statistical Analysis Plan (SAP).

- The primary Safety and Efficacy endpoints of this study are provided in Table 3.
- The secondary Safety endpoints of this study are provided in Table 4.
- The secondary Efficacy endpoints of this study are provided in Table 5.

4.4. Duration of Study Participation

The active study duration for each study participant will be 36 months from HAV implantation. All patients will be followed for the initial 12 months. Beyond 12 months (Long-Term Follow-up), only patients with a patent HAV will be followed out to a total of 36 months from the date of HAV implantation. The total expected duration of the clinical study is 61 months.

5. STUDY POPULATION

5.1. Description of the Study Population

The study population will consist of patients with vascular trauma to size appropriate vessels in the limb or torso, requiring replacement or reconstruction.

Overall recruitment will be restricted to a maximum of 100 patients who receive an HAV implant.

5.1.1. Patient Inclusion Criteria

Patients must satisfy all of these criteria to be eligible for enrollment into the study:

1. Patients with life or limb threatening traumatic injury to an arterial vessel in the limb or torso, other than the heart, which requires replacement or reconstruction.
2. Preoperative imaging or clinical examination indicates the damaged vessel has a defect length of ≤ 38 cm and is appropriately size matched to the 6 mm diameter of the HAV per the judgment of the treating surgeon, taking into account vasoconstriction and situational inflow and outflow considerations.
3. Autologous vein graft is either not feasible in the judgment of the treating surgeon (e.g., because of lack of availability of suitable conduit, presence of severe venous insufficiency) or is not desirable because of the urgency of revascularization.
4. Adults aged 18 to 85 inclusive (all sites) and adolescents who have achieved Tanner Stage V Sexual Maturity Rating (US sites only).
5. Able to communicate meaningfully with investigative staff, and able to comply with entire study procedures. If the patient is unconscious, then information from a reliable witness indicates that the patient would normally be able to comply with study procedures.
6. Patient or legal representative is able, willing and competent to give informed consent.
7. Life expectancy of at least 1 year.

5.1.2. Patient Exclusion Criteria

Patients satisfying any of these criteria will not be eligible to enroll into the study:

1. Mangled Extremity Severity Score (MESS) of ≥ 7.
2. Affected limb is at high risk of amputation despite vascular reconstruction (e.g., because of crush injury).

3. Catastrophic injuries that make survival unlikely (e.g., Abbreviated Injury Scale (AIS) > 5 or Injury Severity Score (ISS) > 60).
4. HAV may not be used for coronary artery repair.
5. Women known to be pregnant.
6. Known medical condition which would preclude long-term antiplatelet therapy after resolution of acute injuries.
7. Any other condition which in the judgment of the investigator would preclude adequate evaluation of the safety and efficacy of the HAV.
8. Previous exposure to HAV.
9. Known participation in any investigational study within the last 30 days.
10. Employees of the Sponsor or patients who are employees or relatives of the Investigator.

5.1.3. Enrollment of Adolescents who have achieved Tanner Stage V Sexual Maturity Rating (US sites only)

The study population includes patients who are assessed to have reached Tanner Stage V by the health care provider. As in adults, vascular injuries in this pediatric population can be treated with the HAV only if the vascular trauma involves size-appropriate vessels, per the judgement of the treating surgeon.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1. Product Description

The Investigational Medicinal Product (IMP) is the Humacyte Human Acellular Vessel (HAV), which is a tissue-engineered vascular prosthesis for vascular bypass or reconstruction in patients with peripheral vascular disease or peripheral vascular trauma.

- The HAV is a sterile, non-pyrogenic, acellular tubular vessel composed of human collagen Type I and Type III, along with other extracellular matrix proteins.
- The HAV is 6 mm in diameter and approximately 42 cm in length.
- The product is supplied on a silicone mandrel immersed in sterile phosphate-buffered saline (PBS) in a sealed and labeled plastic container.
- There is no placebo control or comparator group in this study.

6.2. Manufacturer of the Human Acellular Vessel

Initially, the HAV was manufactured for Humacyte by:

Allosource
6278 S. Troy Circle
Centennial, CO 80111 USA

Since 01July2021, all HAV are now manufactured by:

Humacyte Global, Inc. (previously known as Humacyte, Inc.)
2525 East NC Highway 54
Durham, NC 27713

Traceability of the HAVs during and after the clinical investigation will be achieved by the assignment of lot numbers. A unique identifying lot number is 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 4ºC (range: 2 – 8ºC). The product should be stored in a refrigerator that maintains this temperature range. The HAV must NOT be allowed to freeze.

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

6.4. Implantation of the Human Acellular Vessel (HAV)

The HAV is implanted using standard vascular surgical techniques that are similar to placement of autologous or synthetic peripheral vascular prostheses (see the V005 Study Manual for details).

Tunneling for implantation of the HAV, if required, must be performed using a sheathed tunneler. After inserting the assembled tunneler into the tissue, the inner mandrel of the tunneler should be removed from the sheath. The sheath is lubricated with saline and then with the silicone mandrel in place; the HAV can be easily pushed through the sheath without the need to tie to the inner mandrel and is then pulled through the tunneler (see the V005 Study Manual for details).

After placement, HAV patency and integrity are checked by pressurizing the conduit. Prior to completion of surgery, HAV patency is confirmed by physical examination, Doppler ultrasound evaluation, angiography (conventional or intra-operative CT angiography), or ultrasound. The surgical site is closed using standard techniques.

Implantation of an HAV will be undertaken by qualified vascular surgeons experienced in peripheral vascular surgery.

6.5. HAV Accountability Procedures

Documentation of receipt, dispensing, and return of all HAVs must be maintained by the Principal Investigator or his/her designee. It is the Principal Investigator's responsibility to

ensure that all HAVs are kept in a secure location, with access limited to individuals authorized by the Investigator. The product will be shipped with the HAV Shipment Confirmation Form. Once signed, the form should be returned to Humacyte or authorized designee, and the original will be maintained in the Investigator's Files. The HAV 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. Following accountability of the HAV by Humacyte or their authorized designee, all unused HAVs will be returned to Humacyte.

7. OTHER TREATMENTS AND MEDICATIONS

7.1. Prior and Concomitant Medications

7.1.1. Medication Data to be Collected

For each prior or concomitant reportable medication taken by or administered to the patient, the following information must be collected:

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

7.1.2. Prior Medications

Prior medications are defined as all prescription and over the counter (OTC) medications taken within 7 days before the initial trauma (i.e., prior to Day 1) whether use of that medication was continuing during the study or not.

- All prior and concomitant medications (including immediately pre-surgery and post-surgery medications) must be listed in the patient's medical record.
- Drugs used during anesthesia should be recorded in the anesthesia records but should not be transcribed into the eCRF.
- Drugs used to manage standard issues that may arise during any surgical procedure should not be transcribed into the eCRF, unless they are specifically listed in the reportable medications listed in Table 6.

7.1.3. Concomitant Medications

Concomitant medications are defined as medications taken after the initial trauma, even if this is prior to HAV implantation. Only the concomitant medications described in Table 6 must be recorded on the eCRF.

After HAV implantation, patients should be questioned at each study visit concerning any new medications or changes in current medications. Particular attention should be made to identify the use of antithrombotic or antiplatelet agents.

Table 6 Concomitant Medications That Must Be Recorded in the Patient eCRF

Drug Class	Includes (but is not limited to) These Drugs
Any medications used to manage an adverse event that was considered to be related to the HAV	Any medication satisfying the criterion
Any medications used to manage an adverse event that was considered to be a Serious Adverse Event (SAE)	Any medication satisfying the criterion
Any medications used to manage an adverse event that was considered to be an Adverse Event of Special Interest	Any medication satisfying the criterion
Systemic anti-infective medications (excludes topical, intraocular, local oral treatments such as troche/mouthwash)	Any antibiotic, antifungal, or antiviral medication
Anticoagulant, antiplatelet, or thrombolytic medications	Heparin, warfarin, aspirin, clopidogrel, prasugrel, epoprostenol, dabigatran, rivaroxaban, apixaban, edoxaban, betrixaban, alteplase, direct thrombin inhibitors, factor X_a inhibitors, or vitamin K antagonists
Non-steroidal anti-inflammatory drugs (NSAIDS)	Any medication satisfying the criterion
Systemic glucocorticoids	Any medication satisfying the criterion (excludes those administered by inhalation and those administered by intranasal, topical, or intraocular routes).
Immunomodulatory drugs	Any medication satisfying the criterion
Blood products	Packed red blood cells (RBCs), platelets, fresh frozen plasma, cryoprecipitate, albumin, immunoglobulin
Chemotherapy or Radiation used to treat malignancy	Any medication satisfying the criterion
Lipid lowering agents	Statins, niacin, gemfibrozil, fenofibrate

7.2. Essential, Precautionary and Prohibited Medications

7.2.1. Essential Medications

All patients should receive both antibiotic and antithrombotic prophylaxis in conjunction with HAV implantation in accordance with local hospital guidelines.

Antibiotic prophylaxis: All patients must have at least 1 day of antibiotic prophylaxis initiated on the same day as surgery. Longer antibiotic prophylaxis is at the discretion of the investigator.

Antithrombotic prophylaxis:

- Intraoperative heparin: the doses of heparin to be used during surgery will be determined by the investigator.
- 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 medically appropriate post operatively.
    - Recommended antiplatelet therapy (aspirin 81-325 mg and/or clopidogrel 75 mg daily) is at the discretion of the investigator and should continue long term while the HAV is in place.
    - If the patient is unable to tolerate aspirin and/or clopidogrel the choice of antiplatelet regimen is at the investigator's discretion.

7.2.2. Restricted and Prohibited Medications

Vitamin K antagonists, antiplatelet agents other than aspirin and clopidogrel, direct thrombin inhibitors and factor X_a 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.

8. STUDY PROCEDURES AND EVALUATIONS

8.1. Clinical Evaluations Through Month 12

- Medical History: pre-operatively, from patient / legal representative interview and medical records covering relevant past medical history.
- Smoking History
- Medication History: prescription and OTC medication from Day -7 onwards (see Section 6.7). Particular attention should be paid to the identification of OTC medications containing aspirin.
- Physical Exam: full exam (as far as possible) at pre-operative screening, at the Month 12 Visit, or at the final study visit for early termination (ET). Clinical examination of the operative site and HAV at all post-operative visits; exam of distal vascular bed (extremity injury only); physical exam for lymphadenopathy; additional clinical exam as needed to evaluate adverse events.
- Vital Signs: heart rate, blood pressure and temperature should be obtained at Day 5 after implantation.

- Clinical Laboratories: Blood samples for hematology, clinical chemistry at pre-operative screening and Day 5. Samples for PRA titers should be obtained at pre-operative screening (or within 12 hours of HAV implantation), and at the Day 30, Month 6, and Month 12 Visits.
- Pre-operative Imaging (ultrasound or angiography) is at the discretion of the investigator based on the clinical condition of the patient. It may be omitted if not deemed necessary in order to proceed to vascular surgical repair.
- Adverse Events – post-operatively on Day 1 and at all post-operative visits, the patient will be asked a general question about his/her health and for any HAV problems since the previous visit.
- Post-operative Imaging: Intraoperative HAV bypass or interposition repair exam to assess anastomotic anatomy, patency and runoff. This may include physical exam, Doppler exam, angiography (conventional or intra-operative CT angiography) or ultrasound at the investigator's discretion.
- Duplex ultrasound: clinical assessment must be performed at all postoperative visits from postoperative Day 30 through the Month 12 Visit; HAV patency, mid HAV diameter, and HAV stenosis must be documented. The full length of the HAV should be imaged at each assessment to monitor for aneurysm development.
- Documentation of HAV interventions, surgical procedures, and any complications that occur from the immediate postoperative interval through the Month 12 Visit.

8.2. Clinical Evaluations in Long Term Follow Up (Post Month 12 to Month 36)

The status of the patient and HAV will be ascertained every 3 months after the Month 12 Visit until the Month 36 Visit. Patient status may be ascertained via telephone contact with the patient and/or his physician. If a suspected SAE related to HAV is discovered an unscheduled visit should be conducted to investigate.

Visits at Month 24 and Month 36 are to be conducted in person with a physical exam of the HAV site and duplex ultrasound imaging of the HAV.

Fatal AEs (Deaths) will be reported through the Month 36 Visit.

Only related SAEs and all AESI will be reported.

8.3. Laboratory Evaluations

8.3.1. Clinical and Research Laboratory Evaluations and Specimen Collection

The following parameters will be measured wherever possible at pre-operative screening and all should be measured at Day 5:

- Hematology: hemoglobin, hematocrit, RBC, white blood cells (WBC) with differential, platelet count

- Clinical chemistry: sodium, potassium, calcium, blood urea nitrogen, creatinine, albumin, total bilirubin, glucose (non-fasting)
- PRA titers will be measured at pre-operative screening (or within 12 hours of HAV implantation), at the Day 30 Visit, the Month 6 Visit, and the Month 12 Visit.

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 PRA analysis will be shipped to LabConnect for storage until they are sent for analysis at a central laboratory. Details concerning sample collection and processing can be found in the Study Manual.

8.4. Imaging Evaluations

8.4.1. CT Angiography and Conventional Angiography

CT angiography or conventional angiography will be conducted as pre-operative screening when feasible. Pre-operative imaging is at the discretion of the investigator, based on the clinical condition of the patient. It may be omitted if not deemed necessary in order to proceed to vascular surgical repair.

8.4.2. Duplex Ultrasound

Duplex ultrasound examinations will be performed at Day 30, 3, 6, 9,12, 24, and 36 months and follow standard bypass graft imaging protocols, including B-mode, power Doppler and color duplex ultrasound imaging of the HAV with velocity spectral waveform analysis. The purpose of this duplex ultrasound surveillance is to detect HAV stenosis and aneurysm development. An alternative imaging method (e.g., CTA, MRI, etc.) may be substituted for duplex ultrasound at the discretion of the investigator if it is medically appropriate and in the best interest of the patient.

Determination of intraoperative HAV patency on Day 1 is required by physical examination, Doppler exam, angiography (conventional or intra-operative CT angiography), or ultrasound at the discretion of the investigator.

8.5. Study Schedule

8.5.1. Preoperative Screening (Day 1)

Potential study participants who are being considered for surgical repair of vascular injury appropriate for inclusion into the study 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. If the patient is unable to give informed consent, then this may be sought from the patient's legal representative (usually a close relative). Standard of care procedures such as laboratory evaluations conducted prior to screening may be used rather than repeating the test.

The following assessments will be performed, as far as possible, prior to surgery (Day 1):

- Informed consent
- Medical history
- Prior and concomitant medication
- Full physical examination
- Evaluation of inclusion/exclusion criteria
- Reasons for not using an autologous venous conduit
- Laboratory testing (or standard pre-op lab profile for the institution)
    - Hematology: full blood count and differential
    - Clinical chemistry; sodium, potassium, calcium, blood urea nitrogen, creatinine, albumin, total bilirubin, glucose (non-fasting)
    - PRA titer (if not obtained pre-operatively may be obtained within 12 hr. of surgery)

Ultrasound or CT angiography (CTA) (pre-op imaging is at the discretion of the investigator based on the clinical condition of the patient. It may be omitted if not deemed necessary in order to proceed to vascular surgical repair

8.5.2. Enrollment – Day 1 (HAV Implantation)

The HAV will be implanted as an interposition replacement or bypass in the required location using standard vascular surgical techniques. Details of the surgical anatomy and any complications will be documented. Operative procedures note and surgical diagram will be uploaded into the EDC for medical monitor review. Determination of intraoperative HAV patency is required by physical examination, Doppler exam, angiography (conventional or intra-operative CT angiography), or ultrasound at the discretion of the investigator.

8.5.3. Follow-up Visits Day 5 through Month 12

Day 5 (or prior to hospital discharge if earlier)

The following assessments should be completed:

- Concomitant Medication
- Physical exam including the surgical site
- Vital signs (heart rate, blood pressure and temperature)
- Documentation of any HAV interventions
- Adverse events
- Laboratory assessments (clinical chemistry, hematology)

Day 30 (± 5 days)

The following assessments should be completed:

- Concomitant medication

- Physical exam including the surgical site
- Duplex ultrasound of the HAV
- Documentation of any HAV interventions
- Adverse events
- PRA sample collection

Months 3, 6 and 9 (± 14 days)

The following assessments should be completed:

- Concomitant Medication
- Physical exam including the surgical site
- Duplex ultrasound of the HAV
- Documentation of any HAV interventions
- Adverse events
- PRA sample collection (Month 6 only)

Month 12 (± 14 days) and Early Termination

The following assessments should be completed:

- Concomitant Medication
- Full physical exam including the surgical site
- Duplex ultrasound of the HAV
- Documentation of any HAV interventions
- Adverse events
- PRA (only at early termination if prior to the Month 6 PRA sample collection)
- CT angiography

8.5.4. Long Term Follow-up Post Month 12 through Month 36 (± 30 days)

The status of the patient and HAV will be ascertained every 3 months after the Month 12 Visit up to the Month 36 Visit. The following assessments should be completed:

Quarterly questionnaire covering the status of the patient via a telephone contact with the patient and/or physician. If a suspected SAE related to HAV is discovered an unscheduled visit should be conducted to investigate.

- Documentation of any HAV interventions
- Adverse events (all AESI and related SAEs to be reported)
- Physical exam including surgical site at Month 24 and Month 36

- Duplex ultrasound at Month 24 and Month 36

8.5.5. 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 patient for safety reasons. If withdrawal occurs before 12 months, the patient will be asked to complete an early termination visit at which all assessments normally performed at the Month 12 Visit will be completed. PRA will be collected at ET visit if the visit occurs before Month 6 collection of the sample. If withdrawal occurs after the Month 12 Visit and prior to the Month 36 Visit, 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.

With the exception of patients who withdraw, all patients will be followed for 12 months from HAV implantation (or until HAV removal or death if earlier). The patient should be withdrawn from the study if the HAV is completely removed or the HAV becomes permanently occluded (loss of secondary patency) after Month 12.

8.5.6. 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 Duplex 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.

8.6. Medical Care during the Study and upon Study Termination

Optimal medical therapy should be continued during the study. This should include antiplatelet therapy (see Section 7.2.1)

After the final study visit at Month 36 patients will not receive any further study-specific treatment. They will be treated by their medical doctor in a way that is appropriate for them.

8.7. 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 bypass this should be attempted in accordance with local regulations.

9. 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
- Inflammation at the implantation site
- Adverse events
- Increase from baseline in PRA titers

9.1. Adverse Event Definition

An AE is any untoward medical occurrence in a patient administered an Investigational Medicinal Product (IMP) and which does not necessarily have a causal relationship with the IMP. An AE can, therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the HAV, whether or not the AE is considered to be related to the HAV. 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.

9.2. Serious Adverse Event Definition

An AE is considered to be a Serious Adverse Event (SAE) if it results in any of the following outcomes:

- Death
- Is life-threatening
    - An adverse event is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject or patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
    - Note that hospitalization for the surgery to implant the HAV is not an SAE. However, prolongation of the initial hospitalization due to an AE will be considered an SAE.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening, or require

hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is any adverse drug reaction that is serious (as defined in Section 9.2), 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 HAV caused the adverse event).

9.4. Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) are:

- HAV occlusion (thrombosis)
- HAV spontaneous rupture
- HAV infection
- HAV abandonment
- HAV aneurysm
- HAV pseudoaneurysm
- HAV Excision (partial or complete)

Note that AEs associated with iatrogenic injuries are not considered to be AESI; instead, they should be reported as AEs.

9.5. 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 SAEs should be reported to the Safety CRO within 24 hours from the time the investigator or study personnel first become aware of the event.

AE reporting begins from time of anesthesia induction for implantation of the HAV and ends at the conclusion of the Month 12 Visit or the Early Termination Visit, unless an unresolved AE is still being followed.

During the long term follow up period after the Month 12 Visit through the Month 36 Visit, only the following will be reported by the investigator:

- All SAEs considered related to the HAV
- All Events of Special Interest (Section 9.4)
- All Fatal AEs (deaths)

9.5.1. Causal Relationship to the HAV and the Index Surgical Procedure

The criteria for determining the causal relationship of an AE to the HAV itself, as well as a separate assessment of causal relationship of an AE to the index surgical procedure are required (Table 7). Note that causal relationship to procedure only refers to the index surgical procedure in which the HAV was initially implanted.

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

Table 7 Criteria for Determining Causal Relationship to the HAV or the Index Procedure

Relatedness	Criteria for Relatedness Category
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 patient'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 patient'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.

9.5.2. Criteria for Defining the Severity of an Adverse Event

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

1-Mild: Events require minimal or no treatment and do not interfere with the patient'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 patient'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 patient 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 was related to the AE.

9.5.3. Reporting of Action Taken to Resolve AE

Five categories of actions taken to manage the AE are available for entry in the eCRF:

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

9.5.4. Reporting the Outcome of the AE

Five categories of AE outcomes are available for entry in the eCRF:

- Recovered, with sequelae
- Recovered, without sequelae
- Ongoing
- Death
- Lost to follow-up

9.5.5. 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 patients 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 from postoperative Day 1 through the Month 12 Visit (whether or not causally related to the HAV) must be reported by the investigator or designee to the Safety CRO within 24 hours of learning of its occurrence.

- Any SAE that occurs during Long-term Follow-up (after the Month 12 Visit through the Month 36 Visit) that is considered causally related to the HAV must be reported by the investigator or designee to the Safety CRO within 24 hours of learning of its occurrence.
- Any SAE resulting in patient death (regardless of relatedness attribution) that occurs during Long-term Follow-up (after the Month 12 Visit through the Month 36 Visit) must be reported by the investigator or designee to the Safety CRO within 24 hours of learning of its occurrence.

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 email to the Safety Monitor (see below) IMMEDIATELY (at latest within 24 hours) after becoming aware of the SAE.

Atlantic Research Group, Inc.
Drug Safety Department
Email: Safety@atlanticresearchgroup.com
Telephone: +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.

Copies of relevant portions of 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.

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.

9.5.6. Reporting of Events of Special Interest

Events of Special Interest are defined in Section 9.4 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 3 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 antibiotics (in the case of infections)

9.5.7. Follow-Up of Adverse Events

If any AEs are present when a patient completes 1 year after implantation (i.e., the Month 12 Visit) or the Early Termination Visit (if earlier), or if a patient is withdrawn from the study, the patient 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 patient 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 patient's medical records.

9.6. Reporting of Pregnancy

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

Partner pregnancies do not need to be reported.

9.7. 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.

The DMC will at a minimum meet every 6 months from the date of initial enrollment of the first patient. Additionally, the DMC will review the safety data of the torso injuries on the earlier of when the first torso patient reaches 3 months post-implantation or when the first 2 torso patients have both reached 30 days post-implantation.

10. STATISTICAL CONSIDERATIONS

This is a prospective, open label, nonrandomized multicenter Phase 2/3 study to evaluate the safety and efficacy of the HAV in patients undergoing vascular replacement or reconstruction. There is no formal hypothesis testing planned.

The primary analysis will be conducted when approximately 50 patients complete the 30-day follow-up. Specific details of data handling and analysis will be described in the SAP.

10.1. Analysis Sets

Three Sets of patients will be examined during analysis of study data:

- The **Extremity Set** will include patients who underwent arterial vascular repair with an HAV in an extremity. This population was previously referred to as the "Eligible" population in the Interim Analysis.
- The **All HAV Set** will include all patients who have received an HAV, regardless of the location of the vessel repaired and the type of injury. This population was previously referred to as the "Total" population or the "Safety" population in the Interim Analysis.
- The **Torso+Iatrogenic Set** will include all patients who received an HAV in a location in the Torso as well as any patient who received an HAV to repair an iatrogenic injury. This population was previously referred to as the "Non-Eligible" population in the Interim Analysis.

10.2. Safety Analyses

Safety analyses will be performed on all patients in the Extremity Set (as defined in Section 10.1).

10.2.1. Primary Safety Analyses

Primary Safety Analyses will include the following:

- Rate of HAV infection
- Frequency of Adverse Events of each severity grade.

10.2.2. Secondary Safety Analyses

Secondary safety analyses may focus on evaluating the mechanical stability of the HAV, based on freedom from aneurysmal degeneration, anastomotic bleeding, spontaneous rupture, infection, or significant stenosis. Safety data evaluated to support these analyses may include:

- Adverse Events of Special Interest (AESI) and
- Occurrences of HAV infection.

To determine the durability of the HAV in arterial vascular repair, the rates of interventions needed to maintain or restore HAV patency will be assessed.

In addition, other aspects of HAV function may be assessed for safety, data permitting:

- Amputation rate for the implanted limb
- Patient mortality
- Rate of HAV removal

- Rate of postoperative surgical site infection

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terms.

HAV complications will be listed in terms of incidence, severity, and (where appropriate) time to onset and duration. Additional details will be provided in the SAP.

10.3. Efficacy Analyses

Following discussions with the FDA on 30th March 2022 and in April 2023, the primary Set of patients for analysis of efficacy will be defined as the "Extremity Set", formerly known in the Interim Analysis as the "Eligible population", as defined in Section 10.1.

The sections below provide concise descriptions of the efficacy analyses and endpoints. Specific details will be provided in the SAP.

Primary patency is defined as functional access patency until any type of intervention; primary assisted patency is defined as an HAV still working without complete thrombosis, with or without interventional or surgical procedures to maintain patency; secondary patency is defined as functional HAV patency, with or without preceding successful interventional or surgical procedures to maintain or reestablish patency, until the HAV is abandoned.

10.3.1. Primary Efficacy Analyses

Response will be defined as loss of primary patency before day 30 or maintained primary patency for at least 30 days. The proportion of patients with patency at 30-day will be estimated along with 95% confidence interval. The SAP will describe the estimand approach, including the main estimator and sensitivity analyses.

10.3.2. Secondary Efficacy Analyses

The key secondary efficacy endpoints include secondary patency at 30 days, HAV infection-free rate, and limb salvage rate. For each of these endpoints, the proportion of patients will be estimated along with 95% confidence interval.

Other secondary endpoints include long-term secondary patency, long-term HAV infection-free rate, intervention rates, patient survival and HAV remodeling. Details will be described in the SAP.

10.3.3. Other Analyses

Details of other analysis will be described in the SAP. .

10.4. Sample Size Rationale

Up to 100 patients will be enrolled in the study. The primary efficacy analysis will be performed after approximately 50 patients in the Extremity Set complete the 30-day follow-up. Sample size rationale for primary efficacy analysis will be provided in the SAP.

10.5. Interim Analyses

An interim analysis (IA) was performed using a data cutoff of 22April2022. In this IA, a total of 52 patients were included, of which 34 were in the Extremity Set.

The primary efficacy analysis will be performed after approximately 50 patients in the Extremity Set complete the 30-day follow-up.

11. STUDY MANAGEMENT AND DATA COLLECTION

11.1. 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 and Good Clinical Practice (GCP). Each Investigator will conduct the trial according to applicable local or regional regulatory requirements.

11.2. Institutional Review Board

IRBs must be constituted according to the applicable state and federal requirements, including ICH GCP.

It is the responsibility of each investigator to submit the protocol, Investigator's Brochure, patient informed consent, patient 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 contract research organization (CRO). The documentation should clearly mention the approval/favorable opinion of the protocol, the patient informed consent form, and patient recruitment materials (if applicable), including respective version dates. The written approval and a list of members, their titles or occupations, and their institutional affiliations may be obtained from the IRBs if available, 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 patient informed consent, recruitment materials intended for viewing by patients, 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.

11.3. Patient Informed Consent

Prior to any study procedures being performed, patients and persons conducting the consent discussion will be required to sign and date the IRB-approved informed consent, and each patient will be given a copy. In addition, this information should be recorded in the patient's medical record (i.e., source document). If the patient is unable to give informed consent, then this may be sought from the patient's legal representative, usually a close relative.

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 patient. The investigator or designee shall give the patient 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. Patients must be given ample opportunity to inquire about details of the study.

Pediatric enrollment: Adolescents who have reached Tanner Stage V Sexual Maturity Rating may be enrolled if the vessel to be repaired is size-appropriate (US sites only); this requires obtaining informed consent from the minors legally authorized representative (parental consent or surrogate consent).

11.4. Amendments to the Protocol

An amendment must be agreed to in writing by Humacyte and submitted to the FDA (or other Competent Authorities, if applicable) and approved by the 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 investigator.

11.5. 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 investigator will not be supplied with IMP until all necessary pre-study requirements have been completed and essential signed documents provided to the CRO.

11.6. 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 SOPs and ICH GCP regulations. This includes results of tests performed as a requirement for participation in this study and any other medical records required to confirm information contained in the eCRF such as past medical history and secondary diagnoses. The investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information whenever possible.

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

11.7. Case Report Form

An electronic CRF 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.

11.8. Verification Procedures

It is the investigator's obligation to ensure documentation of all relevant data in the patient's medical record. The patient'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 patient identification code list to enable unambiguous identification of the patients (patient names and corresponding patient numbers). The patient identification code list is an essential document and as such should be maintained according to the ICH GCP guidelines.

11.9. Retention of Records

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

The investigator will maintain a study file, which should be used to file the Investigator's 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 patients, 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 audits 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 patient'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. Patient medical records and other original data will be archived in accordance with the archiving regulations or facilities of the study site.

11.10. 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 patients.

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.

11.11. 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.

11.12. Audits

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 patient's medical records.

12. 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 36 months follow-up. This addendum will be submitted to regulatory authorities in a timely manner.

13. 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.

14. 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.

14.1. 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, and
- 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.

14.2. 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 auditing activities.
- Ensure that all clinical-investigation-related records are retained as specified in this protocol.

14.3. 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.

14.4. Safety Reporting

The principal investigator shall:

- Record every adverse event together with an assessment, in accordance with Section 9 of this protocol,
- Report to the sponsor, without unjustified delay, all serious adverse events and events of special interest as specified in Section 9 of this protocol, and
- Supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting of a particular event.

15. 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.

16. 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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