# Title page

**CLINICAL STUDY REPORT**

**A PHASE 2 ASSESSMENT OF HUMACYTE'S HUMAN ACELLULAR VESSEL IN PATIENTS NEEDING VASCULAR ACCESS FOR DIALYSIS**

**CLN-PRO-V011**
**(Month 3)**

| | |
|---|---|
| Investigational product: | Human acellular vessel |
| Clinical development phase: | 2 |
| Indication: | End-stage renal disease |
| Design: | Prospective, multicenter, open-label, single-arm |
| Sponsor: | Humacyte, Inc.<br>2525 East NC Highway 54<br>Durham, NC 27713, USA |
| Coordinating investigator: | Prof. Wojciech Witkiewicz (Wrocław) |
| Date of first subject enrolled: | 23-Oct-2019 |
| Date of last subject completed Month 3 (data cut-off): | 18-May-2020 |
| Sponsor's signatory: | Kiernan DeAngelis, MD<br>Chief Medical Officer<br>Humacyte Inc. |
| Prepared by: | FGK Clinical Research GmbH<br>Heimeranstr. 35<br>80339 München, Germany |
| Report version and date: | Final 1.0 (15-Feb-2021) |

This study was performed in compliance with Good Clinical Practices (GCP) including the archiving of essential documents

# 1 Synopsis

**Title of the study:**
A Phase 2 Assessment of Humacyte's Human Acellular Vessel in Patients Needing Vascular Access for Dialysis

**Principal investigators and study sites:**
2 investigators at 2 sites in Poland.

**Coordinating investigator:** Prof. Wojciech Witkiewicz (Wrocław)

**Publication (reference):** Not applicable

**Studied period:**
23-Oct-2019 (first subject, first visit) to 18-May-2020 (last subject completing Month 3; data cut-off)

**Clinical phase:** Phase 2

**Objectives:**
***Primary***

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

***Secondary***

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

**Methodology:**
This was a Phase 2, prospective, multicenter, open-label, single-arm study. Subjects who signed informed consent underwent study-specific screening assessments within 45 days from the day of informed consent.

Eligible study subjects received an HAV on Day 0 and are planned to be followed regardless of the HAV patency status to 12 months post implantation at routine study visits at Days 7 and 28, and Months 2, 3, 6, and 12 to assess safety, including immunogenicity, and efficacy of the HAV. After 12 months, only subjects with a patent HAV will be followed (while the HAV remained patent) with study visits every 6 months for up to 3 years (36 months) post implantation.

The primary and main analysis was performed after the last subject completed 3 months of follow-up. Data from this analysis are included in this clinical study report. A second analysis will be performed once all subjects have completed 12 months of follow-up, and a third and final

analysis will be conducted once the last subject has completed 36 months of follow-up. Data from the second and third analyses will be reported in addenda to this main clinical study report.

**Number of subjects (total and for each treatment) planned and analyzed:**

- Planned sample size: Up to 30 subjects implanted with an HAV
- Analysis sets:
  - Intention-to-treat set: 30 subjects
  - Per-protocol set: 30 subjects
  - Safety analysis set: 30 subjects

**Diagnosis and criteria for inclusion:**

1. Subjects with end-stage renal disease (ESRD) who were not, or who were no longer candidates for creation of an autologous arteriovenous (AV) fistula and therefore needed placement of an AV graft in the arm (upper- or forearm) for hemodialysis therapy;
2. Already established on hemodialysis;
3. At least 18 years of age at Screening;
4. Suitable arterial and venous anatomy for implantation of straight or looped conduits in either the forearm or upper arm (not crossing the elbow);
5. Hemoglobin ≥8 g/dL and platelet count ≥100,000 cells/mm³ prior to Day 0 (within 45 days);
6. Other hematological and biochemical parameters within a range consistent with ESRD prior to Day 0 (within 45 days);
7. Normal clotting (international normalized ratio ≤1.5 or prothrombin time ≤18 sec unless the patient was taking an anticoagulant for an approved indication at the time of HAV implantation);
8. Female subjects had to be either:
   a. Of non-childbearing potential, which was defined as post-menopausal (at least 1 year without menses prior to Screening) or documented surgically sterile or post hysterectomy (at least 1 month prior to Screening);
   b. Or, of childbearing potential, in which case:
      i. Must have had a negative serum or urine pregnancy test at Screening, and
      ii. Must have agreed to use at least one form of the following birth control methods for the duration of the study:
         1. Established use of oral, injectable or implanted hormonal methods of contraception;
         2. Placement of an intrauterine device or intrauterine system;
         3. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

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

**Test product and mode of administration:**
The Humacyte HAV is a tissue-engineered vascular conduit for hemodialysis access. HAVs for this study were manufactured using the LUNA commercial manufacturing system. HAVs were implanted into the forearm or upper arm using standard vascular surgical techniques.

**Duration of treatment:** HAV implantation on Day 0; follow-up for this report at 3 months post implantation; planned duration of follow-up is 36 months.

**Criteria for evaluation:**
**Primary endpoints assessed at 3 months post implantation**

***Safety:***

- Adverse events (AEs) indicating possible mechanical failure or weakness of the HAV:
  - Anastomotic rupture
  - Anastomotic bleeding
  - Spontaneous HAV rupture
  - Aneurysm
  - Pseudoaneurysm
  - Abnormal post cannulation hemostasis
- HAV infections
- Change from Baseline of panel reactive antibodies (PRA) and anti-HAV immunoglobulin G (IgG) levels (at 2 months)
- All AEs, serious AEs (SAEs), and AE of special interest

***Efficacy:***

- Primary patency (defined as being maintained until any intervention designed to maintain or reestablish patency, access thrombosis or the measurement of patency, i.e. patent without interventions)
- Primary assisted patency (defined as being maintained until access thrombosis or the time of measurement of patency, including intervening manipulations [surgical or endovascular interventions] designed to maintain the functionality of patent access, i.e. patent without an intervention to clear a thrombus)

- Secondary patency (defined as being maintained until access abandonment [defined as no remaining segment of the HAV is incorporated into the vascular access circuit used for dialysis])

**Secondary endpoints assessed throughout 36-month post-implantation follow-up**

***Safety:***

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

***Efficacy:***

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

**Statistical methods:**

No formal hypothesis testing was done. Data were summarized using descriptive statistics only. HAV patency survival probabilities were calculated using the Kaplan-Meier method.

# SUMMARY - CONCLUSIONS

## Subject disposition

| | |
|---|---|
| Number of prospective subjects screened | 37 |
| Number of subjects enrolled | 30 |
| Number of subjects who received an HAV and completed 3 months of follow-up | 30 |
| Number of subjects who completed 12 months of follow-up | - [a] |
| Number of subjects who are currently being followed | 30 |
| Number of subjects included in the safety and efficacy analyses [b] | 30 |
| Duration of follow-up from implantation of HAV to data cut [18-May-2020] | |
| Median (range): | 166 days (97 – 189 days) |

[a] Study is ongoing; [b] no subject was excluded from the safety analysis set, the intention-to-treat set, or the per-protocol set. Therefore, the analysis sets used are not explicitly specified in the results sections of this report.
HAV = human acellular vessel; "-" = 0.

## Demography and baseline characteristics

| | | | |
|---|---|---|---|
| **Age** [years] | | Median (range) | 67.5 (38 – 88) |
| **BMI** [kg/m$^2$] | | Median (range) | 27.2 (18.6 – 47.0) |
| **Sex** | Male | N (%) | 16 (53.3) |
| | Female | N (%) | 14 (46.7) |
| **Ethnicity** | Not Hispanic or Latino | N (%) | 30 (100) |
| **Race** | White | N (%) | 30 (100) |
| **Duration of renal replacement therapy** [months] | | Median (range) | 70.3 (1 – 333) |
| **Kidney transplant** | Yes | N (%) | 3 (10.0) |
| | No | N (%) | 27 (90.0) |

BMI = body mass index; N = number of subjects.

## Results - efficacy

At Month 3 (Day 91), primary and primary assisted patency was documented for 29 of 30 subjects. In 1 subject, primary patency was lost on the day after the HAV implantation due to thrombosis. According to the responsible sub-investigator, this thrombosis was caused by a technical mistake during the implantation. Secondary patency was observed in all 30 subjects at Month 3.

The following table shows the Kaplan-Meier estimates for 3-month survival of patency. The median time to loss of patency and 6-month survival are not estimable yet, as the majority of subjects has not yet reached 6 months post implantation.

**Survival of graft patency at Month 3: Kaplan-Meier analyses (N=30)**

| | N of subjects with loss of patency | N of subjects remaining at risk | Kaplan-Meier probability of retaining patency [%] | 95% confidence interval |
|---|---|---|---|---|
| Primary patency | 1 | 29 | 96.7 | (78.6; 99.5) |
| Primary assisted patency | 1 | 29 | 96.7 | (78.6; 99.5) |
| Secondary patency | - | 30 | 100 | (100; 100) |

N = number; "-" = 0.

At the time of the data cut (18-May-2020), 5 of 30 subjects had a thrombectomy, angioplasty, or other intervention to maintain patency and usability of the graft. For details, see the following table. All interventions were performed after Month 3, except for one thrombectomy on the day after the HAV implantation.

**Interventions to maintain graft patency and usability (N=30)**

| | Reason | N of subjects (%) | Successful interventions per 100 subject-years |
|---|---|---|---|
| *Any intervention* | - | *5 (16.7)* | *45.0* |
| Any thrombectomy | Thrombosis | 4 (13.3) [a] | 37.5 |
| Any angioplasty | Stenosis | 3 (10.0) | 22.5 |
| Stent, revision, ligation, or HAV removal | - | - | - |
| Other: Placement of hemostat. stitches | Bleeding | 1 (3.3) | N/C |

[a] One subject with 2 thrombectomies.
N = number; N/C = not calculated; "-" = 0.

**Results - safety**

*All* safety data collected until data cut (18-May-2020) are included in this Month 3 report. Notably, the described period extended beyond Month 3 in many cases.

*Extent of exposure:* Thirty subjects received an HAV, which was used for hemodialysis in all 30 subjects. The median duration of HAV exposure was 166 days (range: 97 to 189 days); the median duration of HAV use was 125 days (range: 41 to 151 days).

An overview of the *treatment-emergent AEs* (TEAEs) that occurred during follow-up until data cut-off is given in the tables below. The most frequently reported TEAEs (preferred terms) were vascular access site hematoma, vascular access site thrombosis, and anastomotic stenosis. The latter 2 events were attributed to the HAV in all cases. Other TEAEs attributed to the HAV were vascular graft thromboses and hemodialysis complications.

Eleven (11) TEAEs in 7 subjects were serious, and 8 of these events in 5 subjects were attributed to the HAV. None of the TEAEs were life-threatening or resulted in death or study discontinuation. Most TEAEs were mild or moderate (14 of 20 TEAEs).

No relevant changes in vital signs and clinical laboratory parameters were observed.

**Overall summary of treatment-emergent adverse events (N=30)**

| | N of subjects (%) | N of events [a] |
|---|---|---|
| Subjects with at least one TEAE | 12 (40.0) | 20 |
| TEAEs possibly or definitely related to investigational product | 9 (30) | 14 |
| TEAEs possibly or definitely related to study procedure(s) | 6 (20) | 7 |
| Subjects with at least one serious TEAE | 7 (23.3) | 11 |
| TEAEs resulting in death or study discontinuation | - | - |

Percentages are based on the total number of subjects in the analysis set.
[a] Number of events includes all occurrences of the events.
N = number; TEAE = treatment-emergent adverse event; "-" = 0.

**Treatment-emergent adverse events (MedDRA preferred terms; N=30)**

| MedDRA v20.1 Preferred term | Total number of subjects with TEAE(s) (%) | N of subjects with HAV-related TEAE(s) (%) [a] | N of subjects with procedure-related TEAE(s) (%) [b] | N of subjects with serious TEAE(s) (%) | N of subjects with HAV-related serious TEAE(s) (%) [a] |
|---|---|---|---|---|---|
| *Subjects with any TEAE* | *12 (40.0)* | *9 (30.0)* | *6 (20.0)* | *7 (23.3)* | *5 (16.7)* |
| Vascular access site haematoma | 7 (23.3) | 5 (15.0) | 4 (13.3) | 1 (3.3) | 1 (3.3) |
| Vascular access site thrombosis | 3 (10.0) | 3 (10.0) | 2 (6.7) | 3 (10.0) | 3 (10.0) |
| Anastomotic stenosis | 3 (10.0) | 3 (10.0) | - | 3 (10.0) | 3 (10.0) |
| Vascular graft thrombosis | 1 (3.3) | 1 (3.3) | - | 1 (3.3) | 1 (3.3) |
| Haemodialysis complication | 1 (3.3) | 1 (3.3) | - | - | - |
| Implant site erythema | 1 (3.3) | - | 1 (3.3) | - | - |
| Gastritis | 1 (3.3) | - | - | 1 (3.3) | - |
| Bronchitis | 1 (3.3) | - | - | 1 (3.3) | - |
| Fall | 1 (3.3) | - | - | 1 (3.3) | - |

Percentages are based on the total number of subjects in the analysis set. If a subject had more than one event for a particular term, he or she was counted only once for that term.
[a] Possibly or definitely related to the HAV (study conduit) according to the investigator's assessment; [b] possibly or definitely related to a study procedure according to the investigator's assessment.
HAV = human acellular vessel; MedDRA = Medical Dictionary for Regulatory Activities; N = number; TEAE = treatment-emergent adverse event; "-" = 0.

An overview of the incidence of TEAEs of special interest is given in the table below.

**Treatment-emergent adverse events of special interest (N=30)**

| | N of subjects | N of events | Time to event [days] Median (range) |
|---|---|---|---|
| HAV thrombosis | 4 | 5 | 141 (2 – 154) |
| Clinically significant HAV stenoses | 3 | 3 | 142 (139 – 156) |
| HAV anastomotic bleeding | 1 | 1 | 186 (-) |
| HAV infection | - | - | - |
| Spontaneous HAV or anastomotic rupture | - | - | - |
| HAV aneurysms or pseudoaneurysms | - | - | - |
| TEAEs leading to revision of the HAV | - | - | - |
| TEAEs resulting in HAV abandonment | 1 | 1 | 149 (-) |

HAV = human acellular vessel; N = number; TEAE = treatment-emergent adverse event; "-" = 0.

**Immunogenicity**

A total of 14 (47%) subjects had pre-existing Class I and/or Class II PRA at Baseline, and 28 out of 30 subjects (93%) had PRA values that remained at baseline levels. Through Month 2, 2 subjects (7%) exhibited Class I PRA levels that were elevated from Baseline. There have been no reported AEs or prior transplantations in either subject which could explain the PRA elevations; the cause of the elevations is thus far unknown. The cause of PRA elevations for both subjects is not clearly related to the HAV. However, this percentage is consistent with previous clinical studies of the HAV in patients requiring hemodialysis (6%).

**Conclusions:**

- At Month 3, primary patency and primary assisted patency were maintained in 29 of 30 subjects, and all subjects showed secondary graft patency.
- HAV infections and indications of mechanical failure or weakness of the HAV were not observed.
- The percentage of subjects who exhibited elevation from Baseline in Class I PRA levels at Month 2 (7%) is consistent with previous clinical studies of Aura- or Terra-produced HAVs in patients requiring hemodialysis (6%).
- Overall, the results of the LUNA-produced HAV to date do not indicate any particular safety or immunogenicity issues.

**Date of report:** 15-Feb-2021