# Title page

**CLINICAL STUDY REPORT ADDENDUM - SUMMARY**

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

**(12-MONTH FOLLOW-UP REPORT)**

Protocol Number: CLN-PRO-V011

| | |
|---|---|
| Study 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 |
| Principal investigators | Prof. Wojciech Witkiewicz (Wrocław) |
| Date of first subject enrolled: | 23-Oct-2019 |
| Date of last subject completed 12-month follow-up: | 04-Feb-2021 |
| Sponsor's signatory: | Kiernan DeAngelis, MD<br>Chief Medical Officer<br>Humacyte, Inc. |
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| Report version and date: | Final 1.0 (07-Sep-2021) |

This study was performed in compliance with Good Clinical Practice guidelines including the archiving of essential documents. This report must be kept strictly confidential. Disclosure of the contents (in whole or in part) to third parties is permissible only with written consent of Humacyte, Inc.

# 1 Investigational plan

## 1.1 Overall study design and plan

This was a Phase 2, prospective, multicenter, open-label, single-arm study in subjects with end-stage renal disease (ESRD) who required hemodialysis and were targeted for implantation of an arteriovenous graft for dialysis access.

A total of 30 eligible subjects were enrolled, received a human acellular vessel (HAV) on Day 0, and were followed up for 12 months post-implantation regardless of the HAV's patency status at routine study visits scheduled at Day 7, Day 28, Month 2, Month 3, Month 6 and Month 12. After 12 months, only subjects with a patent HAV will be followed up (while the HAV remains patent) at study visits every 6 months for up to 3 years (36 months).

The primary analysis was performed after the last subject completed 3 months of follow-up (FU). Data from this analysis (data cut-off 18-May-2020) are included in the main clinical study report (CSR; CLN-PRO-V011 Month 3). A second analysis was performed after all subjects have completed 12 months of FU. Data of this analysis are included in this CSR addendum. The final analysis will be performed after the last subject has completed 36 months of FU, and will be reported in a separate CSR addendum.

## 1.2 Objectives and endpoints

### 1.2.1 Objectives

**Primary *(reported in the main CSR)***

To evaluate the safety, efficacy, and immunogenicity over 3 months after implantation of 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.

### 1.2.2 Endpoints

The primary endpoints were assessed at 3 months post implantation and are reported in the main CSR (CLN-PRO-V011 Month 3).

Secondary endpoints assessed at Months 6 and 12 (where applicable; see T-Table 1), are reported in this CSR addendum.

**Secondary endpoints assessed throughout 36-month post-implantation FU**

***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 antibody (PRA) and anti-HAV immunoglobulin G (IgG) levels (at 12 months)
- All AEs and serious adverse events (SAEs) until 12 months post implantation, after that only SAEs associated with the HAV and adverse events of special interest (AESIs)

***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)

## 1.3 Overview of data collection

The schedule of assessments is provided in T-Table 1.

**T-Table 1: Schedule of assessments**

| | Screening D-45 to D0 | D0 | D7[9] | D28 | M2 | M3 | M6, M12 | M18-36 (every 6M) | | ET[10] |
|---|---|---|---|---|---|---|---|---|---|---|
| Visit window | -- | -- | +8 D | ±7 D | ±7 D | ±7 D | ±14 D | ±1 M | | -- |
| Informed consent | X | | | | | | | | | |
| Demographics | X | | | | | | | | | |
| Medical history | X | X | | | | | | | | |
| Concomitant medications[1] | X | X | X | X | X | X | X | | | X |
| Physical exam., temperature[2] | X | (X) | (X) | (X) | (X) | (X) | (X) | (X) | | (X) |
| Electrocardiogram (12-lead) | X | | | | | | | | | |
| Vessel mapping[3] | X | | | | | | | | | |
| Central vein stenosis | X | | | | | | | | | |
| Confirm eligibility [4] | X | X | | | | | | | | |
| HAV placement | | X | | | | | | | | |
| Laboratory assesments[5] | X | | | X | X | | | | | |
| PRA / anti-HAV IgG | X | | | X | X | | X | | | X |
| Surgical site healing | | | X | X | | | | | | |
| Access site and HAV exam. | | | X | X | X | X | X | X | | X |
| HAV patency[6] | | X | X | X | X | X | X | X | | X |
| Duplex ultrasound | | | | X | X | X | X | X | | X |
| Suitability of HAV for dialysis | | | | X | X | X | X | X | | |
| Removal of pre-implantation CVC (if applicable) | | | X | X | X | X | | | | X |
| Hemodialysis/CVC use | | | X | X | X | X | X | X | | X |
| AEs / AEs of special interest [7] | X | X | X | X | X | X | X | X | | X |

Only assessments highlighted in grey are reported in this CSR addendum.

[1] All prescription medications and aspirin taken in the 7 days before surgery (Day 0) and during the study up to Month 12.

[2] At Screening, a complete physical examination was performed At all other visits, temperature was obtained and symptom-directed physical examinations were performed as appropriate (denoted as (X)).

[3] If adequately undertaken within 8 weeks before Screening with no significant change in the condition of the subject (including insertion of CVC), repeat vessel mapping was at the discretion of the principal investigator. Vessel mapping performed by ultrasound in the clinic by the investigator was acceptable.

[4] Before implantation, the screening data were reviewed by the principal investigator and the medical monitor to confirm eligibility.

[5] Hematology and chemistry. At Screening also INR (or prothrombin time, if INR value was not available) and a serum or urine pregnancy dipstick test for women of childbearing potential. Standard of care laboratory evaluations conducted before consent could be used to determine eligibility if conducted within the screening period time window.

[6] Duplex ultrasound was used after Day 7 (+ 8 days) to assess patency, diameter of the lumen mid-conduit and flow rate and to monitor aneurysm development.

[7] During the screening period, only SAEs related to the screening procedures were reported. From Day 0 after implantation up to Month 12, all AEs were reported.

[9] Anytime from Day 7 to 15.

[10] Subjects withdrawn before the Month 36 visit were to have ET assessments performed. Subjects withdrawn before Month 12 were to complete an ET correlating with the procedures at Month 12.

AE = adverse event, CVC = central venous catheter, D = day, ET = early termination, exam. = examination, HAV = human acellular vessel, IgG = immunoglobulin G, INR = international normalized ratio, M = month(s), PRA = panel reactive antibody, SAE = serious adverse event, screen. = Screening.

## 1.4 Description of study days

Study assessments up to Month 12 were performed as listed in T-Table 1. Further FU visits are scheduled every 6 months up to Month 36 and will be reported separately.

## 1.5 Safety and efficacy assessments

### 1.5.1 Assessments of safety

#### 1.5.1.1 Adverse events

All AEs occurring between Day 0 after implantation and 1 year post implantation (Month 12 visit) or early termination visit, whichever occurred earlier, were to be reported.

Definitions of AEs, SAEs, and suspected unexpected serious adverse reactions are provided in Sections 9.1, 9.2, and 9.2.1, respectively, of the protocol. AEs were coded using the Medical Dictionary for Regulatory Activities Version 20.1.

**Adverse events of special interest**

Adverse events of special interest related to interventions and infections included the following:

- Events resulting in HAV abandonment
- HAV thrombosis
- HAV infection
- HAV aneurysm (HAV lumen diameter >9 mm) formation
- Clinically significant HAV pseudoaneurysm (clinically significant defined as requiring a surgical or radiological intervention)
- HAV spontaneous rupture

  *Note: Iatrogenic injuries were not considered events of special interest and were to be reported as AEs.*
- Events resulting in HAV revision or ligation
- Events resulting in HAV removal
- Clinically significant stenosis of HAV (clinically significant defined as severity of severe or greater, or requiring a surgical or radiological intervention)
- Clinically significant Steal Syndrome (clinically significant defined as severity of severe or greater, or requiring a surgical or radiological intervention)

- Anastomotic bleeding
- Anastomotic rupture

**Relationship to the investigational product or procedure**

Separate assessments of causal relationship of an AE to the HAV and to HAV implantation was required. Causal relationship to procedure only refers to the index surgical procedure during which the HAV was initially implanted.

Criteria for determining the causal relationship are provided in Section 9.4 of the protocol.

**Severity**

All AEs were assessed according to the criteria described in Section 9.5 of the protocol.

#### 1.5.1.2 Safety laboratory assessments

Laboratory tests were performed as scheduled in T-Table 1. No clinical safety laboratory was assessed after the Month 2 visit. The following laboratory assessments were performed between Month 3 and Month 12:

- PRA
- IgG antibodies to graft extracellular matrix material (Humacyte IgG assay)

Blood samples for PRA/anti-HAV IgG analysis were analyzed at the central laboratory.

#### 1.5.1.3 Physical examination

Symptom-directed physical examinations were conducted as needed. The body temperature was measured at all visits.

Assessments of surgical site healing and clinical examinations of the access site and HAV were performed as scheduled in T-Table 1.

#### 1.5.1.4 Other safety assessments

The time to the first cannulation with the HAV was recorded, as well as data on dialysis access use, on any post-implantation renal transplants during the study, and on clinical examination of access site.

### 1.5.2 Assessment of efficacy

Duplex ultrasound was used to assess patency, diameter of the lumen mid-conduit and flow rate, and to monitor aneurysm development as scheduled in T-Table 1. Interventions to maintain or

restore patency were recorded. Histopathological remodeling of the HAV was analyzed based on collected samples (if applicable).

Patency was defined as:

- **Primary patency:** being maintained until any intervention designed to maintain or re-establish patency, access thrombosis or the measurement of patency, i.e., patent without interventions
- **Primary assisted patency:** 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:** being maintained until access abandonment (i.e., no remaining segment of the HAV is incorporated into the vascular access circuit used for dialysis)

### 1.6 Statistical analysis

Details on the statistical analyses are provided in the statistical analysis plan (SAP). Only analyses of secondary endpoints are briefly described in the following.

#### 1.6.1 Secondary efficacy analyses

All secondary efficacy analyses were based on the intention-to-treat set, which includes all enrolled subjects. Time to loss of patency was analyzed by the Kaplan-Meier method (detail provided in the SAP). Interventions to maintain patency included anything performed at one session. For example, thrombectomy plus angioplasty at one session were considered as a single intervention.

Subgroup analyses of patency and total interventions were performed by sex and study site.

Analysis of histopathological remodeling of HAV was performed by Humacyte.

#### 1.6.2 Secondary safety analyses

Treatment-emergent AEs (TEAEs) constituted those AEs with onset after the start of the anesthesia for the implant surgery. TEAEs were summarized by system organ class and preferred term.

Continuous laboratory values were summarized using raw data and change from baseline values at each time point. All other safety data were summarized.

### 1.7 Changes in the conduct of the study or planned analyses

The first protocol version under which subjects were included was protocol Version 1.2, dated 18-Dec-2018. The protocol was not amended.

A protocol administrative change letter was issued:

- Letter #1, dated 18-Jan-2020: clarified that AEs of special interest requiring surgical or radiological intervention were to be considered serious and reported using the same process and timeline as for SAEs.

The planned analyses were not changed.

## 2 Results - study subjects

The results sections of this CSR addendum reflect data collected until 04-Feb-2021 (last subject's Month 12 visit date; referred to as 'data cut-off'). Data already reported in the main CSR without changes since, are not reported herein.

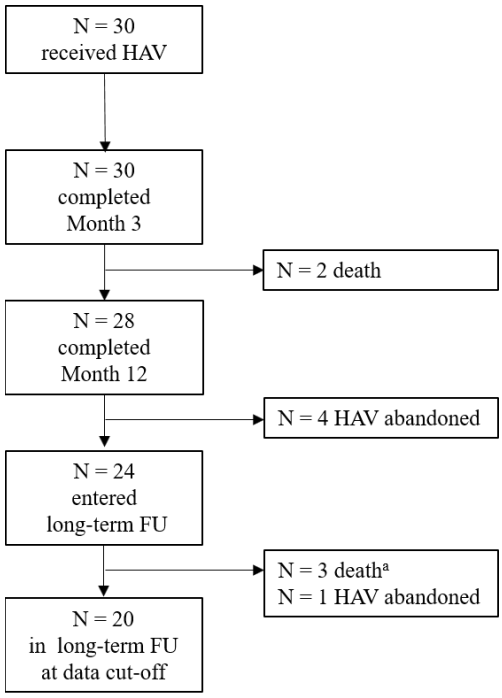
At data cut-off, some subjects had already completed later visits.

### 2.1 Disposition of subjects

The study started on 23-Oct-2019 (first subject, first visit) and is expected to end in Nov-2022 (last subject, completion Month 36 visit).

An overview of the subject disposition is shown in T-Figure 1. Of the 30 subjects who were included, received an HAV, and completed Month 3, 28 subjects completed the Month 12 visit. 2 subjects died between Month 3 and Month 12. 24 subjects continued long-term FU, as in 4 subjects the HAV was abandoned at Month 12. No subject had completed 36 months at the time of data cut-off. 3 subjects died and for 1 subject the HAV was abandoned during long-term FU until data cut-off.

**T-Figure 1: Subject disposition**




[a] One subject died after Month 12 due to an adverse event with unknown start date. This event is reported as part of the Month 12 data.

FU = follow-up, HAV = human acellular vessel, N = number of subjects.

As all 30 enrolled subjects were included for analysis in the intention-to-treat, per-protocol, and safety analysis set, analysis sets are not differentiated in the following description of results.

## 2.2 Protocol deviation

Protocol deviations were documented for 27 of the 30 subjects (90%), of which 15 subjects had 23 major protocol deviations. Major protocol deviations included 16 cases of delayed SAE reporting (deviation category 'safety') in 11 subjects (36.7%), of which 10 cases in 7 subjects were reported after data cut-off for the Month 3 analysis. All other major protocol deviations (Month 3 visits not done and Month 3 study procedure not done) are reported in the main CSR (CLN-PRO-V011 Month 3).

None of the major deviations led to exclusion of the subjects from the per-protocol set as the deviations were not related to efficacy data or substantially impacted subject safety. Minor protocol deviations were mostly due to coronavirus disease 2019 (COVID-19)-related problems (visits not done or done outside the visit window, or study procedures not done).

## 2.3 Concomitant medications

An overview of the concomitant medications used during the study (including antibiotics mainly given in conjunction with HAV implantation) is given in T-Table 2. Most frequently used (i.e., by more than 50% of subjects) were antibiotics and antithrombotic agents (all subjects), beta blocking agents (67%), and diuretics (53%).

**T-Table 2: Concomitant medication (used by more than 1 subject; N = 30)**

| ATC2 | Number (%) of subjects | ATC preferred terms (n) |
|---|---|---|
| Antibacterials for systemic use | 30 (100) | Cefazolin (15); ceftriaxone sodium (10); ceftriaxone (6); vanomycin (2); amoxicillin (1); clindamycin (1)[a] |
| Antithrombotic agents | 30 (100) | Acetylsalicylic acid (24); acenocoumarol (3); clopidogrel (2); enoxaparin (2); enoxaparin sodium (1); heparin (1); ticlopidine (1); warfarin (1) |
| Beta blocking agents | 20 (66.7) | Bisoprolol (9); metoprolol (5); nebivolol (4); carvedilol (3); atenolol (1) |
| Diuretics | 16 (53.3) | Furosemide (13); torasemide (3) |
| Antihypertensives | 14 (46.7) | Clonidine (9); doxazosin (5); methyldopa (1) |
| Drugs for acid related disorders | 13 (43.3) | Pantoprazole (7); omeprazole (5); pantoprazole sodium sesquihydrate (1) |
| Mineral supplements | 13 (43.3) | Calcium (6); calcium carbonate (6); magnesium (1); potassium (1) |
| Calcium channel blockers | 12 (40.0) | Nitrendipine (5); lercanidipine (4); amlodipine (3) |
| Lipid modifying agents | 12 (40.0) | Atorvastatin (11); simvastatin (1) |
| Drugs used in diabetes | 9 (30.0) | Insulin human (4); insulin detemir (2); insulin human, insulin human injection, isophane (2); insulin aspart (1); insulin lispro (1); insulin lispro, insulin lispro protamine suspension (1) |
| Vitamins | 8 (26.7) | Alfacalcidol (5); vitamin D NOS (2); vitamin B NOS (1) |
| Agents acting on the renin-angiotensin system | 8 (26.7) | Ramipril (6); valsartan (2); captopril (1); lisinopril (1) |
| Antianaemic preparations | 6 (20.0) | Folic acid (4); ferrous sulfate (1); iron (1) |
| Analgesics | 6 (20.0) | Paracetamol, tramadol hydrochloride (2); tramadol hydrochloride (2); tramadol (1); caffeine, codeine, paracatemol (1); paracetamol (1); gabapentin (1) |
| Antigout preparations | 4 (13.3) | Allopurinol (4) |
| Cardiac therapy | 4 (13.3) | Amiodarone (3); digoxin (1) |
| Drugs for obstructive airway diseases | 4 (13.3) | Budesonide; fenoterol (1); fenoterol, ipratropium (1); ipratropium (1); ipratropium bromide (1); montelukast (1); salbutamol (1) |
| Psycholeptics | 3 (10.0) | Hydroxyzine (2); midazolam (1); zolpidem (1); zopiclone (1) |
| Antiinflammatory products | 2 (6.7) | Diclofenac (1); indometacin (1) |
| Calcium homeostasis | 2 (6.7) | Cinacalcet (2) |
| Corticosteroids for systemic use | 2 (6.7) | Methylprednisolone (1); prednisone (1) |
| Digestives, incl. enzymes | 2 (6.7) | Pancreatin (2) |
| Vasoprotectives | 2 (6.7) | Calcium dobesilate (1); lidocaine, tribenoside (1) |
| All other therapeutic products | 2 (6.7) | Calcium carbonate (2) |

[a] In main clinical study report: 1 subject each with ciprofloxacin and clavulanic acid; however, these were prior medications and are not included herein.

ATC(2) = World Health Organization Anatomical Therapeutic Chemical drug classification system (2nd level term), incl. = including, N = number of subjects in the analysis set, n = number of subjects using the respective medication, NOS = no other specification.

# 3 Results - safety

## 3.1 Extent of exposure

All 30 enrolled subjects received an HAV and had it successfully used for hemodialysis. The median duration of the HAV exposure (from implantation until early termination, complete removal, or data cut-off) was 418.5 days (range: 338 to 450 days), corresponding to 33.7 subject-years. The median duration of the HAV use for hemodialysis (from first cannulation until abandonment, transplant, early termination, complete removal, or data cut-off) amounted to 348.5 days (range: 110 to 413 days), corresponding to 27.0 subject.

## 3.2 Adverse events

### 3.2.1 Brief summary of adverse events

A brief summary of the TEAEs observed during FU is given in T-Table 3. In total, 25 subjects (83%) experienced 70 TEAEs. Of these, 49 TEAEs were possibly or definitely related to the HAV, and 7 TEAEs possibly or definitely related to study procedures. 19 subjects experienced 48 serious TEAEs, of which 3 events were life-threatening and 3 events resulted in death. Most TEAEs were mild or moderate (47 of 70 TEAEs).

**T-Table 3: Summary of treatment-emergent adverse events (N = 30)**

| | Number (%)[a] of subjects | Number of events |
|---|---|---|
| **Any TEAE** | **25 (83.3)** | **70** |
| **Relationship of TEAE to HAV** | | |
| Not related | 4 (13.3) | 18 |
| Unlikely related | 1 (3.3) | 3 |
| Possibly related | 6 (20.0) | 15 |
| Definitely related | 14 (46.7) | 34 |
| **Relationship of TEAE to study procedure(s)** | | |
| Not related | 19 (63.3) | 63 |
| Possibly related | 2 (6.7) | 3 |
| Definitely related | 4 (13.3) | 4 |
| **Severity** | | |
| Mild | 7 (23.3) | 26 |
| Moderate | 5 (16.7) | 21 |
| Severe | 9 (30.0) | 17 |
| Life-threatening | 1 (3.3) | 3 [b] |
| Death | 3 (10.0) | 3 |
| **TEAEs leading to death** | **3 (10.0)** | **3** |
| **TESAE** | **19 (63.3)** | **48** |

At relationship and severity level, subjects reporting more than 1 TEAE were counted only once with the strongest relationship and maximum severity.
[a] Percentages are based on N.
[b] Two subjects with 1 life-threatening event each also had 1 event each of severity 'death'.
HAV = human acellular vessel, N = number of subjects in the analysis set, TEAE = treatment-emergent adverse event, TESAE = treatment-emergent serious adverse event.

### 3.2.2 Display of adverse events

An overview of all TEAEs reported until data cut-off is provided in T-Table 4. Vascular access site thrombosis (11 subjects), anastomotic stenosis (8 subjects), vascular access site hematoma (7 subjects), vascular access site pseudoaneurysm (5 subjects), and vascular stenosis (4 subjects) were the most frequently reported TEAEs. All other TEAEs, but coronavirus infection reported in 2 subjects, were reported in 1 subject each.

**T-Table 4: Treatment-emergent adverse events by system organ class and preferred term (N = 30)**

| System organ class<br>Preferred term | Number (%)[a] of subjects | |
|---|---|---|
| **Any TEAE** | **25** | **(83.3)** |
| **Cardiac disorders** | **2** | **(6.7)** |
| Bradycardia | 1 | (3.3) |
| Cardiac failure | 1 | (3.3) |
| Ventricular tachycardia | 1 | (3.3) |
| **Gastrointestinal disorders** | **1** | **(3.3)** |
| Gastritis | 1 | (3.3) |
| Haemorrhoids | 1 | (3.3) |
| **General disorders and administration site conditions** | **1** | (3.3) |
| Implant site erythema | 1 | (3.3) |
| **Infections and infestations** | **8** | **(26.7)** |
| Bacterial sepsis | 1 | (3.3) |
| Bronchitis | 1 | (3.3) |
| Clostridium difficile infection | 1 | (3.3) |
| Coronavirus infection | 2 | (6.7) |
| Diabetic foot infection | 1 | (3.3) |
| Haematoma infection | 1 | (3.3) |
| Localised infection | 1 | (3.3) |
| Vascular access site infection | 1 | (3.3) |
| **Injury, poisoning and procedural complications** | **21** | **(70.0)** |
| Anastomotic stenosis | 8 | (26.7) |
| Fall | 1 | (3.3) |
| Vascular access site haematoma | 7 | (23.3) |
| Vascular access site haemorrhage | 1 | (3.3) |
| Vascular access site pseudoaneurysm | 5 | (16.7) |
| Vascular access site thrombosis | 11 | (36.7) |

*continued*

**T-Table 4: Treatment-emergent adverse events by system organ class and preferred term (N = 30) *(continued)***

| System organ class<br>Preferred term | Number (%)[a] of subjects | |
|---|---|---|
| **Metabolism and nutrition disorders** | **1** | (3.3) |
| Hypercholesterolaemia | 1 | (3.3) |
| **Musculoskeletal and connective tissue disorders** | **1** | (3.3) |
| Ischaemic stroke | 1 | (3.3) |
| **Vascular disorders** | **5** | **(16.7)** |
| Brachiocephalic vein stenosis | 1 | (3.3) |
| Vascular stenosis | 4 | (13.3) |

[a] Percentages are based on N.
N = number of subjects in the analysis set, TEAE = treatment-emergent adverse event.

### 3.2.3 Analysis of adverse events

#### Intensity

Most TEAEs (47 of 70) were mild or moderate and 17 (in 9 subjects) were severe (T-Table 3). In total, 3 subjects had 1 life-threatening TEAE each (*Clostridium difficile* infection, coronavirus infection, bacterial sepsis) and 3 subjects died (cardiac failure, coronavirus infection [2 subjects]).

#### Relation to the HAV

20 subjects had 49 TEAEs possibly or definitely related to the HAV (T-Table 3). An overview of all TEAEs with relationship to the HAV is provided in T-Table 5. The most frequently reported TEAEs related to the HAV were vascular access site thrombosis (in 11 subjects), anastomotic stenosis (in 8 subjects), and vascular access site hematoma and pseudoaneurysm (in 5 subjects each).

**T-Table 5: Treatment-emergent adverse events with possible or definite relationship to HAV by system organ class and preferred term (N = 30)**

| System organ class | Number (%)[a] of subjects with TEAEs with relation to HAV assessed as | |
|---|---|---|
| Preferred term | possible | definite |
| **Any TEAE** | **6 (20.0)** | **14 (46.7)** |
| **Infections and infestations** | **1 (3.3)** | **1 (3.3)** |
| Haematoma infection | - | 1 (3.3) |
| Vascular access site infection | 1 (3.3) | - |
| **Injury, poisoning and procedural complications** | **7 (23.3)** | **13 (43.3)** |
| Anastomotic stenosis | 3 (10.0) | 5 (16.7) |
| Vascular access site haematoma | 4 (13.3) | 1 (3.3) |
| Vascular access site haemorrhage | - | 1 (3.3) |
| Vascular access site pseudoaneurysm | 1 (3.3) | 4 (13.3) |
| Vascular access site thrombosis | 1 (3.3) | 10 (33.3) |
| **Vascular disorders** | **-** | **4 (13.3)** |
| Vascular stenosis | - | 4 (13.3) |

Subjects with multiple events for one preferred term were only counted once (with the strongest relationship). '-' = 0.
[a] Percentages are based on N.
HAV= human acellular vessel, N = number of subjects in the analysis set, TEAE = treatment-emergent adverse event.

The investigator assessed TEAEs in 6 subjects as possibly or definitely related to study procedures (vascular access site hematoma [4 subjects], vascular access site thrombosis [2 subjects], implant site erythema [1 subject]).

### Outcome

The outcome of most TEAEs was "recovered/resolved" (52 events) or "recovered/resolved with sequelae" (2 events)*;* 10 TEAEs were "unresolved" at data cut-off, 3 TEAEs were" ongoing at time of death", and for 3 TEAEs the outcome was "death".

## 3.3 Deaths, other serious adverse events, and other significant adverse events

### 3.3.1 Deaths

In total, 3 TEAEs staring before Month 12 resulted in the death of the subjects (cardiac failure [1 subject], coronavirus infection [2 subjects]; T-Table 6). One of these subjects died during the long-term FU after Month 12, but the TEAE leading to death (coronavirus infection) may have already started before the Month 12 visit (unknown start date). None of the events were assessed as related to the HAV.

**T-Table 6: Treatment-emergent adverse events leading to death (N = 30)**

| Preferred term (verbatim) | Start day | Day of death | Relationship to HAV |
|---|---|---|---|
| Cardiac arrest (heart failure) | Unknown[a] | Day 338 | Not related |
| Coronavirus infection (recurrent COVID-19 infection) | Day 331 | Day 385 | Not related |
| Coronavirus infection (severe COVID-19 infection resulting in death) | Day 344 | Day 358 | Not related |

[a] The event started in 2020 with unknown exact start date.
COVID-19 = coronavirus disease 2019, HAV = human acellular vessel, N = number of subjects in the analysis set.

Two additional subjects died of TEAEs during the long-term FU after Month 12, thus, at the time of data cut-off 5 subjects had died.

### 3.3.2 Other serious adverse events

In total, 48 serious TEAEs were reported in 19 subjects (T-Table 3; T-Table 7), and 34 TESAEs in 13 subjects were possibly or definitely related to the HAV. The most frequently reported TESAEs (in ≥10% of subjects) were vascular access site thrombosis, anastomotic stenosis, vascular stenosis, and vascular access site pseudoaneurysm, all of which were assessed as possibly or definitely related to the HAV. Three SAEs were life-threatening (*Clostridium difficile* infection, coronavirus infection, bacterial infection) and 3 events caused the subject's death (cardiac failure, coronavirus infection [2 events]; T-Table 6).

**T-Table 7: Treatment-emergent serious adverse events by preferred term (N = 30)**

| | Number (%)[a] of subjects | |
|---|---|---|
| **Preferred term** | **with TESAE(s)** | **with HAV-related[b] TESAE(s)** |
| **Any (related) TESAE** | **19 (63.3)** | **13 (43.3)** |
| Vascular access site thrombosis[c] | 10 (33.3) | 10 (33.3) |
| Anastomotic stenosis | 6 (20.0) | 6 (20.0) |
| Vascular stenosis | 4 (13.3) | 4 (13.3) |
| Vascular access site pseudoaneurysm | 3 (10.0) | 3 (10.0) |
| Haematoma infection | 1 (3.3) | 1 (3.3) |
| Vascular access site infection | 1 (3.3) | 1 (3.3) |
| Vascular access site haematoma | 1 (3.3) | 1 (3.3) |
| *Coronavirus infection* | *2 (6.7)* | - |
| Bradycardia | 1 (3.3) | - |
| *Cardiac failure* | *1 (3.3)* | - |
| Gastritis | 1 (3.3) | - |
| Bacterial sepsis | 1 (3.3) | - |
| Bronchitis | 1 (3.3) | - |
| Clostridium difficile infection | 1 (3.3) | - |
| Diabetic foot infection | 1 (3.3) | - |
| Localised infection | 1 (3.3) | - |
| Fall | 1 (3.3) | - |
| Ischaemic stroke | 1 (3.3) | - |
| Brachiocephalic vein stenosis | 1 (3.3) | - |

For subjects with multiple events for one preferred term, only the strongest relationship was counted. Events shown in *italics* led to the death of the subject. '-' = 0.

[a] Percentages are based on N.

[b] With possible or definite relationship.

[c] In the main clinical study report, one of these was reported as "vascular graft thrombosis"; since then, the wording was changed to vascular access site thrombosis.

HAV= human acellular vessel, N = number of subjects in the analysis set, TESAE = treatment-emergent serious adverse event.

### 3.3.3 Adverse events of special interest and other significant adverse events

#### 3.3.3.1 Overview adverse events of special interest

The incidence of AESIs as assessed by the investigators is summarized in T-Table 8. Most frequently reported (in ≥10% of subjects) were vascular access site thrombosis, anastomotic stenosis, vascular access site pseudoaneurysm, and vascular stenosis.

**T-Table 8: Adverse events of special interest by preferred term (N = 30)**

| Preferred term | Number (%)[a] of subjects | |
|---|---|---|
| **Any AESI** | **15** | **(50.0)** |
| Vascular access site thrombosis | 11 | (36.7) |
| Anastomotic stenosis[b] | 6 | (20.0) |
| Vascular access site pseudoaneurysm | 5 | (16.7) |
| Vascular stenosis | 4 | (13.3) |
| Haematoma infection | 1 | (3.3) |
| Brachiocephalic vein stenosis | 1 | (3.3) |

AESIs include all AEs for which the AESI box in the eCRF page was ticked. N = 0 is shown as '-'.
[a] Percentages are based on N.
[b] Only events with reported interventions until data cut-off were considered as AESIs.
AESI = adverse event of special interest, eCRF = electronic case report form, N = number of subjects in the analysis set.

### 3.3.3.2 Analysis of adverse events of special interest

#### 3.3.3.2.1 HAV thrombosis

19 HAV thromboses were reported in 11 subjects (37%), corresponding to a rate of 60 thromboses per 100 subject-years of retaining secondary patency. The median time to onset of the first HAV thrombosis was 218 days (range: 2 to 406 days).

#### 3.3.3.2.2 HAV infections

No HAV-related infections were reported.

#### 3.3.3.2.3 Clinically significant HAV stenoses

15 clinically significant stenoses (i.e., with severity of severe or greater, or requiring a surgical or radiological intervention) were observed in 9 subjects (30%; 10 mild, 4 moderate, and 1 severe stenosis), corresponding to a rate of 47 stenoses per 100 subject-years of retaining secondary patency. The median time to onset of the first stenosis was 285 days (range: 139 to 360 days).

#### 3.3.3.2.4 Spontaneous HAV rupture and anastomotic rupture

No spontaneous HAV ruptures or anastomotic ruptures were reported.

#### 3.3.3.2.5 HAV anastomotic bleeding

No HAV anastomotic bleeding was reported.[1]

[1] One event of HAV anastomotic bleeding was reported in the main CSR, but was changed to not being of special interest in the meantime.

#### 3.3.3.2.6 HAV aneurysms and pseudoaneurysms

No aneurysm was observed. In 5 subjects (17%), 5 HAV pseudoaneurysms were observed, corresponding to a rate of 16 pseudoaneurysms per 100 subject-years of retaining secondary patency. The median time to the first occurrence of a pseudoaneurysm was 356 days (range: 308 to 383 days).

#### 3.3.3.2.7 TEAEs leading to revision of the HAV

One vascular access site thrombosis, which was reported as a serious TEAE, led to revision of the HAV at Day 435.

### 3.3.3.3 TEAEs leading to abandonment or removal of the HAV

Only 1 TEAE (pseudoaneurysm) led to the partial removal of the HAV. In 7 subjects (23%), the HAV was abandoned due to thromboses (6 subjects) or failed surgical revision to restore patency (1 subject). HAVs were abandoned between Day 149 and Day 435.

## 3.4 Clinical laboratory evaluation

Clinical laboratory was only evaluated until Month 2 and is reported in the main CSR (CLN-PRO-V011 Month 3).

## 3.5 Other safety data

### 3.5.1 Vital signs

No relevant changes were observed.

### 3.5.2 Post-implantation renal transplants

None of the subjects received a renal transplant during the study.

### 3.5.3 Cannulation of the HAV and dialysis catheter use

The HAV was ready for dialysis in 29 subjects at Day 28 and in 1 subject at Month 3. In all subjects, the HAV was used for dialysis. The median time to the first successful 2-needle cannulation of the HAV was 42.5 days (range: 29 to 169 days). At the time of data cut-off, 9 subjects (30%) have had a new dialysis access or catheter inserted post HAV implantation.

### 3.5.4 Examination of access site

Thrill and bruit were present in all subjects examined at all visits, except in 2 of 29 subjects at Month 6, and in 4 of 27 subjects at Month 12. Findings at examination of the access sites are

summarized in T-Table 9. No problems at the surgical incision or HAV site were detected at Month 3 and Month 12.

**T-Table 9: Access site findings (N = 30)**

| Visit | Finding | Number (%)[a] of subjects | |
|---|---|---|---|
| Day 7 (N = 30) | **Abnormal surgical incision** | **1** | **(3.3)** |
| | Erythema | 1 | (3.3) |
| | Hematoma | 1 | (3.3) |
| Day 28 (N = 30) | **Abnormal surgical incision** | **3** | **(10.0)** |
| | Hematoma | 3 | (10.0) |
| Month 2 (n=29) | **Abnormal HAV site** | **1** | **(3.4)** |
| | Localized hematoma | 1 | (3.4) |
| Month 6 (n=29) | **Abnormal HAV site** | **2** | **(6.9)** |
| | Localized hematoma | 1 | (3.4) |
| | Other[b] | 1 | (3.4) |

[a] Percentages are based on n.
[b] HAV thrombosis.
HAV = human acellular vessel, N = number of subjects in the analysis set, n = number of subjects at each visit.

### 3.5.5 Physical examination

As per protocol, symptom-directed physical examinations were only to be conducted as appropriate No symptom-directed examinations were performed.

### 3.5.6 Immunogenicity

Of the 30 subjects who were implanted with an HAV, 14 subjects (47%) had pre-existing Class I and/or Class II PRA at Baseline. During FU, PRA levels were elevated from Baseline in 10 subjects (33%); in 4 of these subjects, PRA levels subsequently returned to the respective baseline calculated PRA levels or below. Two additional subjects exhibited a reduction in calculated PRA levels after the respective elevation. In total, 4 subjects (13%) had an increase in PRA levels from Baseline that remained elevated through Month 12.

De novo PRA specificities were determined to be either Class I PRA (6 subjects, 20%) or Class II PRA (4 subjects, 13%), with 2 subjects exhibiting a single matching de novo PRA specificity with their respective HAV donor cell HLA phenotype (both Class I HLA-B7).

## 3.6 Safety summary

During the first year after HAV implantation, 25 of 30 subjects (83%) experienced TEAEs (70 events in total), and in 20 of these subjects the TEAEs were possibly or definitely related to the HAV. The most frequently reported AEs were vascular access site thrombosis (11 subjects),

anastomotic stenosis (8 subjects), vascular access site hematoma (7 subjects), vascular access site pseudoaneurysm (5 subjects), and vascular stenosis (4 subjects). Most AEs were mild or moderate. 17 severe AEs were reported in 9 subjects, of which 14 were reported as TESAEs. 3 subjects had 1 life-threatening TEAE each (*Clostridium difficile* infection, coronavirus infection, bacterial sepsis). 2 of these subjects died (cardiac failure, coronavirus infection). Another subject died of coronavirus infection. No relationship to the HAV was reported for the life-threatening events or the deaths. Two additional subjects died of TEAEs during the long-term FU after Month 12; thus, at the time of data cut-off 5 subjects had died.

HAV infections and indications of mechanical failure or weakness of the HAV, e.g., spontaneous HAV ruptures, and aneurysms were not observed. In 5 subjects, HAV pseudoaneurysms occurred with a median time to the first occurrence being 356 days (range: 308 to 383 days).

No relevant changes in body temperature were observed. The HAV was used for dialysis in all subjects.

Of the 30 subjects who were implanted with an HAV, 14 subjects (47%) had pre-existing Class I and/or Class II PRA at Baseline. During FU, PRA levels were elevated from Baseline in 10 subjects (33%); in 4 subjects (13%), PRA levels remained elevated through Month 12.

# 4 Results - efficacy

## 4.1 Patency

At Month 12, primary patency was documented in 17 subjects, primary assisted patency in 19 subjects, and secondary patency in 23 subjects (T-Table 10). The Kaplan-Meier probabilities to retain patency at Month 12 were 60.0% for primary, 67% for primary assisted, and 83% for secondary patency. The time to loss of primary and primary assisted patency ranged from 2 to 357 days, and time to loss of secondary patency from 149 to 435 . Corresponding Kaplan-Meier curves are shown in T-Figure 2.

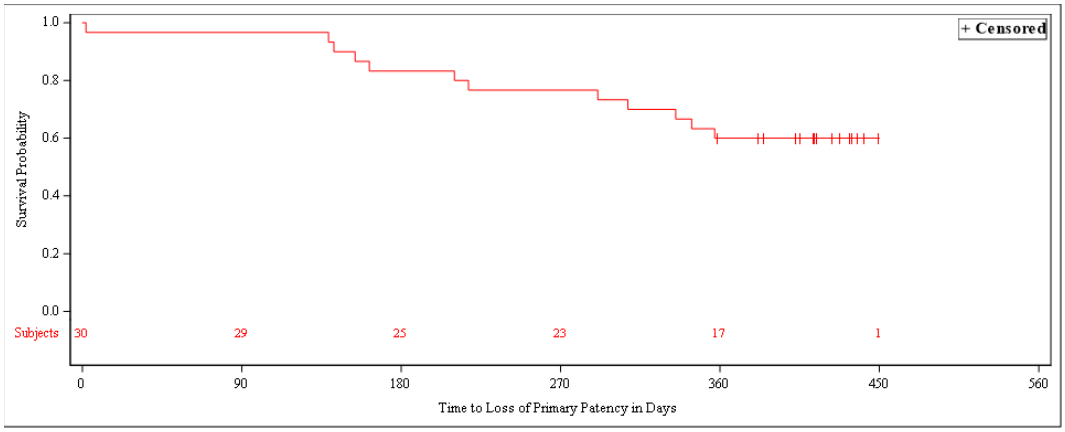
**T-Table 10: Kaplan-Meier estimates of time to loss of patency (N = 30)**

| Patency | Primary | | | Primary assisted | | | Secondary | | |
|---|---|---|---|---|---|---|---|---|---|
| Visit | n | Pr [%] | (95% CI) | n | Pr [%] | (95% CI) | n | Pr [%] | (95% CI) |
| Month 3 (Day 91) | 29 | 96.7 | (78.6, 99.5) | 29 | 96.7 | (78.6, 99.5) | 30 | 100 | (100, 100) |
| Month 6 (Day 182) | 25 | 83.3 | (64.5, 92.7) | 25 | 83.3 | (64.5, 92.7) | 28 | 93.3 | (75.9, 98.3) |
| Month 12 (Day 365) | 17 | 60.0 | (40.5, 75.0) | 19 | 66.7 | (46.9, 80.5) | 23 | 83.2 | (64.2, 92.6) |

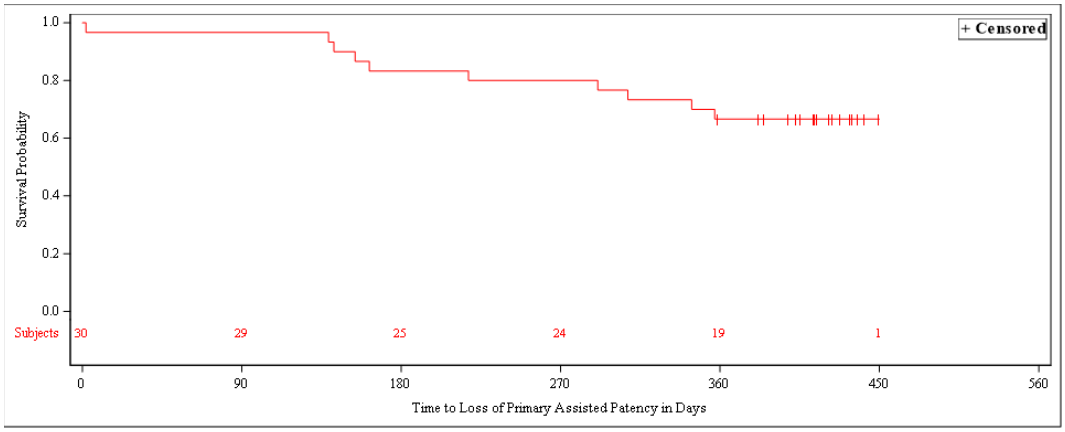
Subjects who discontinued early, died, or were transplanted with the graft still patent were censored at that time point. Data of subjects without loss of patency were censored at data cut-off.
CI = confidence interval, N = number of subjects in the analysis set, n = number of subjects at risk, Pr = graft patency probability.

**T-Figure 2: Kaplan-Meier curves of time to loss of graft patency (N = 30)**

**(A) Primary patency**



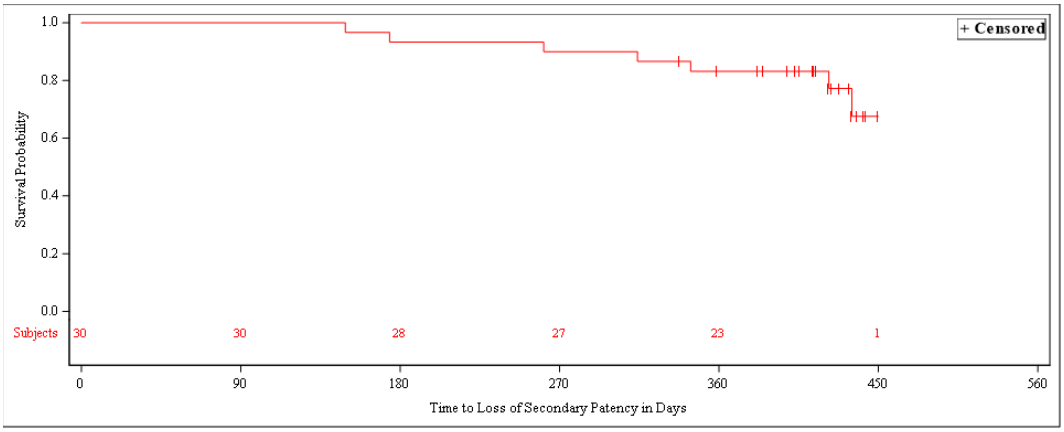

**(B) Primary assisted patency**




*continued*

**T-Figure 2: Kaplan-Meier curves of time to loss of graft patency (N = 30) (continued)**

**(C) Secondary patency**




Subjects who discontinued early, died, or were transplanted with the graft still patent were censored at that time point. Data of subjects without loss of patency were censored at data cut-off.
N = number of subjects in the analysis set.

Patency rates by sex are shown in T-Table 11. At Month 12, patency rates of women were slightly lower than of men with 57.1% vs 62.5% for primary, 64.3% vs 68.8% for primary assisted, and 77.9% vs 87.5% for secondary patency. Corresponding Kaplan-Meier curves are shown in T-Figure 3.

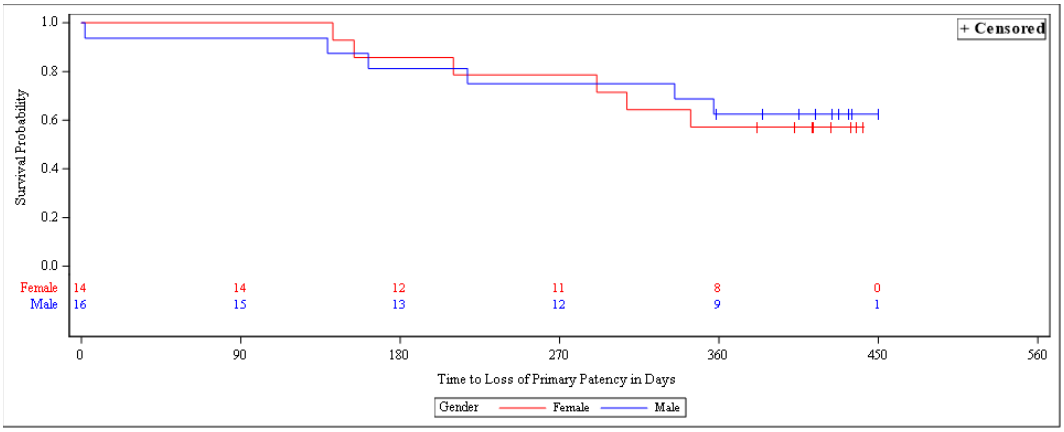
**T-Table 11: Kaplan-Meier estimates of time to loss of patency by sex (N = 30)**

| Patency by sex<br>Visit | Primary | | | Primary assisted | | | Secondary | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Pr [%] | 95% CI | n | Pr [%] | 95% CI | n | Pr [%] | 95% CI |
| **Women** | | | | | | | | | |
| Month 3 (Day 91) | 14 | 100 | (100, 100) | 14 | 100 | (100, 100) | 14 | 100 | (100, 100) |
| Month 6 (Day 182) | 12 | 85.7 | (53.9, 96.2) | 12 | 85.7 | (53.9, 96.2) | 13 | 92.9 | (59.1, 99.0) |
| Month 12 (Day 365) | 8 | 57.1 | (28.4, 78.0) | 9 | 64.3 | (34.3, 83.3) | 10 | 77.9 | (45.9, 92.3) |
| **Men** | | | | | | | | | |
| Month 3 (Day 91) | 15 | 93.8 | (63.2, 99.1) | 15 | 93.8 | (63.2, 99.1) | 16 | 100 | (100, 100) |
| Month 6 (Day 182) | 13 | 81.3 | (52.5, 93.5) | 13 | 81.3 | (52.5, 93.5) | 15 | 93.8 | (63.2, 99.1) |
| Month 12 (Day 365) | 9 | 62.5 | (34.9., 81.1) | 10 | 68.8 | (40.5, 85.6) | 13 | 87.5 | (58.6, 96.7) |

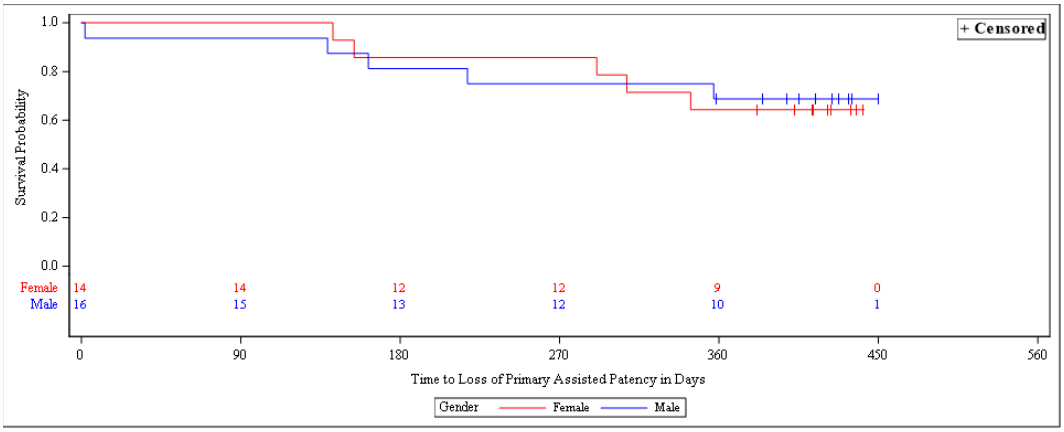
Subjects who discontinued early, died, or were transplanted with the graft still patent were censored at that time point. Data of subjects without loss of patency were censored at data cut-off.
CI = confidence interval, N = number of subjects in the analysis set, n = number of subjects at risk, Pr = graft patency probability.

## T-Figure 3: Kaplan-Meier curves of time to loss of graft patency by sex (N = 30)

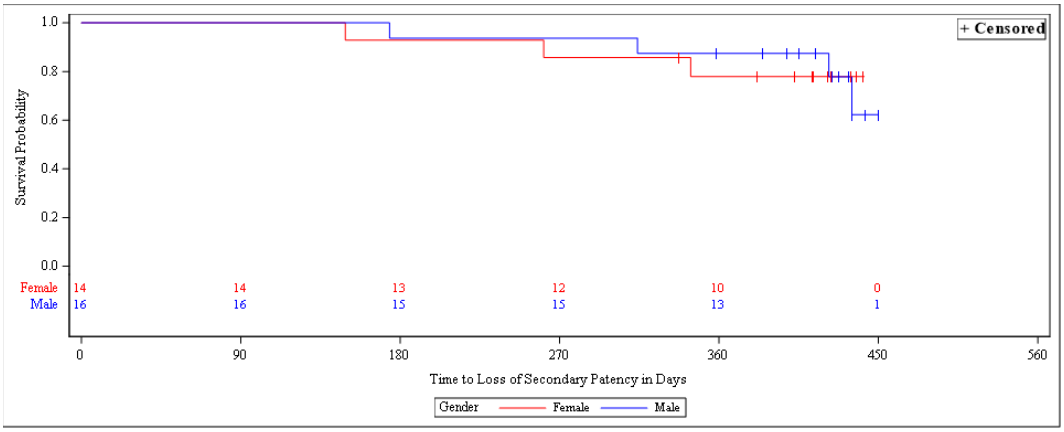
### (A) Primary patency




### (B) Primary assisted patency




### (C) Secondary patency




Subjects who discontinued early, died, or were transplanted with the graft still patent were censored at that time point. Data of subjects without loss of patency were censored at data cut-off.
N = number of subjects in the analysis set.

The results of subgroup analyses by study site showed no apparent differences between study sites.

## 4.2 Other efficacy endpoints

Until data cut-off, 14 subjects had an intervention performed to maintain patency and usability of the graft, corresponding to 84.8 successful interventions per 100 subject-years (T-Table 12). None of the subjects needed a stent or revision to maintain secondary patency. No graft ligation was performed, but 1 HAV was first partially removed and then permanently abandoned due to failed surgical revision to restore patency on Day 435. The HAV graft was permanently abandoned in 6 further subjects due to thromboses between Day 149 and Day 422.

**T-Table 12: Interventions to maintain patency and usability of the graft (N = 30)**

| | Number (%)[a] of subjects | Number of interventions | Successful interventions per 100 subject-years (overall) |
|---|---|---|---|
| **Any intervention** | **14 (46.7)** | **30** | **84.8** |
| Any thrombectomy | 9 (30.0) | 12[b] | 37.7 |
| Any angioplasty | 10 (33.3) | 15[b,c] | 47.1 |
| Stent, revision, ligation | - | | - |
| HAV removal (partial) and debridement | 1 (3.3) | 1 | n.c. |
| Other[d] | 5 (16.7) | 5 | n.c. |

'-' = 0.

[a] Percentages are based on N.

[b] 3 subjects with 2 interventions. [c] 1 subject with 3 interventions.

[d] Debridement of soft tissue; removal of pseudoaneurysm with reconstruction of bovine patch; placement of homeostatic stitches; thrombectomy and bovine patch plasty; resections of the aneurysm with bovine pericardium patch plasty.

HAV = human acellular vessel, N = number of subjects in the analysis set, n.c. = not calculated.

An overview of the blood flow rates and graft diameters determined by ultrasound during the study is given in T-Table 13. Median flow rates were comparable between Day 28 and Month 3, with a slight decrease in slow rate at Month 6 and Month 12. Similarly, the median inner mid-conduit diameter remained similar to the nominal starting inner diameter of 6 mm between Day 28 and Month 3 with a decrease at Month 6 and Month 12.

**T-Table 13: Ultrasound examination of the HAV: Flow rate and diameter (N = 30)**

| | Visit | n | Median | (Range) |
|---|---|---|---|---|
| **Flow rate [mL/min]** | Day 28 | 30 | 1490 | (449 - 2530) |
| | Month 2 | 26 | 1400 | (600 -2304) |
| | Month 3 | 17 | 1590 | (500 - 2659) |
| | Month 6 | 28 | 1110 | (0 - 2466) |
| | Month 12 | 27 | 1000 | (0 - 2600) |
| **Inner diameter mid-conduit [mm]** | Day 28 | 30 | 5.9 | (5.3 - 6.7) |
| | Month 2 | 26 | 5.9 | (5.2 - 6.3) |
| | Month 3 | 17 | 5.9 | (5.5 - 6.3) |
| | Month 6 | 28 | 5.8 | (0.0 - 6.2) |
| | Month 12 | 27 | 5.8 | (0.0 - 6.5) |

HAV = human acellular vessel, N = number of subjects in the analysis set, n = number of subjects with available data.

Overall, 9 subjects (30%) received a new dialysis access or catheter after the implantation (1 new access each in 6 subjects and 2 accesses in 3 subjects each). In 2 of these subjects, the new dialysis access was used intermittently, i.e., for both the HAV is still used as dialysis access.

## 4.3 Efficacy summary

At Month 12 (Day 365), primary patency was observed in 17 subjects (57%), primary assisted patency in 19 subjects (63%), and secondary graft patency in 23 subjects (77%). The Kaplan-Meier probabilities to retain patency at Month 12 were 60% for primary, 67% for primary assisted, and 83% for secondary patency.

Until data cut-off, 14 subjects had at least 1 intervention performed to maintain patency and usability of the graft, corresponding to 84.8 successful interventions per 100 subject-years. None of the subjects needed a stent or revision to maintain secondary patency. In total, 7 HAV grafts were permanently abandoned between Day 149 and Day 422 due to thromboses (in 6 subjects) or failed surgical revision (1 subject).

# 5 Conclusions

- At Month 12, primary patency and primary assisted patency were maintained in 17 and 19 subjects, respectively, and 23 subjects still showed secondary graft patency.
- HAV infections and indications of mechanical failure or weakness of the HAV were not observed.
- The proportion of subjects who exhibited elevation from Baseline in PRA levels at Month 12 (33%) is higher than in previous clinical studies of Aura- or Terra-produced HAVs in patients requiring hemodialysis (6%). However, PRA levels decreased subsequently in 6 subjects (in 4 subjects to baseline levels or below), and remained elevated in 4 subjects (13%) through Month 12.
- Overall, the results of the LUNA-produced HAV to date do not indicate any particular safety or immunogenicity issues.