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CLINICAL STUDY REPORT ADDENDUM - SUMMARY

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

(24-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 Global, Inc. 2525 East NC Highway 54 Durham, NC 27713, USA
Principal investigators	Prof. Wojciech Witkiewicz (Wrocław)
Date of first patient enrolled:	23-Oct-2019
Date of last patient completed Month 24 follow-up:	02-Mar-2022
Sponsor's signatory:	Shamik Parikh Chief Medical Officer Humacyte Global, Inc.
Prepared by:	FGK Clinical Research GmbH Heimeranstr. 35, 80339 München, Germany
Report version and date:	Final 1.0 (26-Apr-2023)

1 Investigational plan

1.1 Overall study design and plan

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

A total of 30 eligible patients 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 patients with a patent HAV were followed up (while the HAV remained patent) at study visits every 6 months. The long-term follow-up (FU) was planned to extend to 3 years (36 months), but it was decided to reduce the duration of the total study to 24 months for all patients.

The primary analysis was performed after the last patient completed 3 months of FU and data from that analysis (data cut-off 18-May-2020) were included in the main clinical study report (CSR; CLN-PRO-V011 Month 3). A second analysis was performed at 12 months (CSR addendum CLN-PRO-V011 Month 12). The final analysis was performed after the last patient had completed 24 months of FU, and results are reported in this 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]

[1] As per protocol administration change letter #2, the HAV was followed up to 24 months after implantation.

1.2.2 Endpoints

The primary endpoints were assessed at 3 months post implantation and were reported in the main CSR (CLN-PRO-V011 Month 3). Secondary endpoints assessed at Months 6 and 12 (as applicable; see T-Table 1), were reported in a CSR addendum (CSR addendum CLN-PRO-V011 Month 12). Secondary endpoints assessed every 6 months throughout the long-term FU up until Month 24 (ie, Month 18 and Month 24) are reported in this CSR addendum

Secondary endpoints assessed throughout 24 months[2] post implantation of the HAV

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.

[2] Originally planned for up to 36 months (see protocol administrative change letter #2, Section 1.7).

T-Table 1: Schedule of assessments

	Screening D-45 to D0	D0	D7[8]	D28	M2	M3	M6, M12	M18-36* (every 6M)		ET[9]
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

* Originally planned until M36. Was changed with protocol administrative change letter #2 to end at M24 (see Section 1.7).
Only assessments highlighted in gray 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 patient (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. During the long-term follow-up period from Month 12 to Month 24 post implantation, only related SAEs and ESIs were documented.

[8] Anytime from Day 7 to 15.

[9] Patients withdrawn between Month 12 and Month 36 visit were to complete an ET correlating with the procedures at Month 36.

AE = adverse event, CVC = central venous catheter, D = day, ESI = event of special interest, 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 24 were performed as listed in T-Table 1. At completion of the last patient's Month 24 visit, the study was terminated as per Sponsor request.

1.5 Safety and efficacy assessments

1.5.1 Assessments of safety

1.5.1.1 Adverse events

During the long-term FU period from 12 to 24 months after implantation, only related SAEs and events of special interest (see definition below), were to be reported.

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

AESIs

AESIs 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 assessment 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

No laboratory assessments or PRA/anti-HAV IgG analyses were scheduled after Month 12 (see T-Table 1).

1.5.1.3 Physical examination

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

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, ie, 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, ie, patent without an intervention to clear a thrombus
- **Secondary patency:** being maintained until access abandonment (ie, 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). As primary endpoints were reported at Month 3, the following subsections briefly describe secondary analyses.

1.6.1 Secondary efficacy analyses

All secondary efficacy analyses were based on the intention-to-treat set, which includes all enrolled patients. Time to loss of patency was analyzed by the Kaplan-Meier method (detail provided in the SAP). Interventions to maintain patency included all types of interventions performed in one session. For example, thrombectomy plus angioplasty in 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 for any explanted HAV samples was performed by the Sponsor.

1.6.2 Secondary safety analyses

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

All other safety data were summarized.

1.7 Changes in the conduct of the study or planned analyses

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

Two protocol administrative change letters were 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
- Letter #2, dated 21-Jan-2022: informed investigators and regulatory authorities of the Sponsor's decision to end the study participation of patients at the completion of 24 months

The planned analyses were not changed.

2 Results - study patients

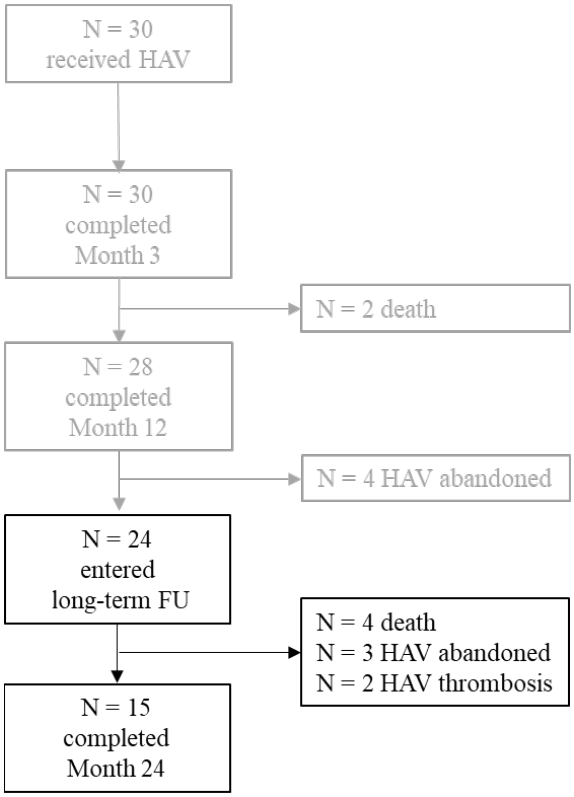
2.1 Disposition of patients

The study started on 23-Oct-2019 (first patient, first visit) and prematurely (ie, not as per protocol) ended on 02-Mar-2022 (last patient, completion Month 24 visit) after decision by the Sponsor to end the study at completion of Month 24.

An overview of the patient disposition is shown in T-Figure 1. Of the 30 patients who were included, received an HAV, and completed Month 3, 28 patients completed the Month 12 visit (2 patients died before Month 12).

24 of these 28 patients had a patent HAV at the end of Month 12 (HAV was abandoned in 4 patients before Month 12) and continued in the long-term FU. 9 patients discontinued early (ie, before Month 24) during long-term FU: 4 patients died, the HAV was abandoned in 3 patients, and the HAV thrombosed and led to discontinuation in 2 patients. 15 of these 24 patients completed the study at Month 24.

T-Figure 1: Patient disposition



Data shown in gray were already reported in the previous CSR addendum.
CSR = clinical study report, FU = follow-up, HAV = human acellular vessel, N = number of patients.

As all 30 enrolled patients 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 29 of the 30 patients (96.7%), of which 20 patients (66.7%) had at least 1 major protocol deviation. Most major protocol deviations were related to safety, ie, delays in SAE reporting (17 patients, 56.7%).

None of the major deviations led to exclusion of the patients from the per-protocol set as the deviations were not related to efficacy data or substantially impacted patient safety. Minor protocol deviations were reported in 28 patients (93.3%) and mostly involved coronavirus disease 2019 (COVID-19)-related problems (in 22 patients, 73.3%), such as visit not done, visit done outside the visit window, or study procedures not done.

2.3 Concomitant medications

Data on concomitant medication were only recorded up until Month 12 and not during the long-term FU (T-Table 1). Medications taken until and including Month 12 are reported in the previous report. All patients received antibacterials for systemic use and antithrombotic agents.

3 Results - safety

3.1 Extent of exposure

All 30 enrolled patients received an HAV and had it successfully used for hemodialysis. The duration of the HAV exposure (from implantation until early termination, complete removal, data cut, or end of study) was a median of 691.5 days (range: 338 to 827 days), corresponding to 49.1 patient-years. The duration of the HAV use for hemodialysis (from first cannulation until abandonment, transplant, early termination, complete removal, or end of study) amounted to a median of 563.5 days (range: 110 to 785 days), corresponding to 42.4 patient-years.

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 2. In total, 29 patients (96.7%) experienced 103 TEAEs. Of these, 81 TEAEs in 26 patients were possibly or definitely related to the HAV, and 7 TEAEs possibly or definitely related to study procedures. 24 patients (80.0%) experienced 78 treatment-emergent serious adverse events (TESAEs), of which 3 events were life-threatening and 4 events resulted in death. Most TEAEs (76 of 103) were mild or moderate.

T-Table 2: Summary of treatment-emergent adverse events (N = 30)

	Number (%)[a] of patients[b]	Number of events[c]
Any TEAE	**29 (96.7)**	**103**
Relationship of TEAE to HAV		
Not related	2 (6.7)	19
Unlikely related	1 (3.3)	3
Possibly related	8 (26.7)	35
Definitely related	18 (60.0)	46
Relationship of TEAE to study procedure(s)		
Not related	23 (76.6)	96
Possibly related	2 (6.7)	3
Definitely related	4 (13.3)	4
Severity		
Mild	6 (20.0)	40
Moderate	9 (30.0)	36
Severe	9 (30.0)	20
Life-threatening	1 (3.3)[d]	3[b]
Death	4 (13.3)	4
TEAEs leading to death	**4 (13.3)**	**4**
TESAE	**24 (80.0)**	**78**

[a] Percentages are based on N.
[b] Patients reporting more than 1 TEAE were counted only once with the strongest relationship and maximum severity.
[c] Includes all occurrences of events.
[d] Two additional patients who had a life-threatening event also had an event leading to death and were only counted for the latter events.
HAV = human acellular vessel, N = number of patients 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 is provided in T-Table 3. Vascular access site thrombosis (18 patients), anastomotic stenosis (11 patients), vascular access site hematoma (8 patients), vascular stenosis (7 patients), and vascular access site pseudoaneurysm (5 patients) were reported by 5 or more patients. All other TEAEs, but coronavirus infection (reported in 2 patients), were reported in 1 patient each.

T-Table 3: Treatment-emergent adverse events by system organ class and preferred term (N = 30)

System organ class Preferred term	Number (%)[a] of patients	
Any TEAE	**29**	**(96.7)**
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	**27**	**(90.0)**
Anastomotic stenosis	11	(36.7)
Fall	1	(3.3)
Vascular access site complication	1	(3.3)
Vascular access site haematoma	8	(26.7)
Vascular access site haemorrhage	1	(3.3)
Vascular access site pseudoaneurysm	5	(16.7)
Vascular access site thrombosis	18	(60.0)
Metabolism and nutrition disorders	**1**	(3.3)
Hypercholesterolaemia	1	(3.3)
Musculoskeletal and connective tissue disorders	**1**	(3.3)
Arthritis	1	(3.3)
Nervous system disorders	1	(3.3)
Ischaemic stroke	1	(3.3)
Vascular disorders	**8**	**(26.7)**
Brachiocephalic vein stenosis	1	(3.3)
Vascular stenosis	7	(23.3)

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

3.2.3 Analysis of adverse events

Intensity

Most TEAEs (76 of 103) were mild or moderate and 20 TEAEs (in 9 patients) were severe (T-Table 2). In total, 3 patients had 1 life-threatening TEAE each (*Clostridium difficile* infection, coronavirus infection, bacterial sepsis)[3] and 4 patients died (cardiac failure, coronavirus infection [2 patients], and respiratory insufficiency).

Relation to the HAV

26 patients had 81 TEAEs possibly or definitely related to the HAV (T-Table 2). An overview of all TEAEs with relationship to the HAV is provided in T-Table 4. The most frequently reported TEAEs related to the HAV were vascular access site thrombosis (in 18 patients), anastomotic stenosis (in 11 patients), vascular stenosis (in 7 patients), vascular access site hematoma (in 6 patients), and pseudoaneurysm (in 5 patients).

T-Table 4: 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 patients with TEAEs with relation to HAV assessed as	
Preferred term	possible	definite
Any TEAE	**8 (26.7)**	**18 (60.0)**
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	**9 (30.0)**	**17 (56.7)**
Anastomotic stenosis	6 (20.0)	5 (16.7)
Vascular access site complication	1 (3.3)	-
Vascular access site haematoma	4 (13.3)	2 (6.7)
Vascular access site haemorrhage	-	1 (3.3)
Vascular access site pseudoaneurysm	1 (3.3)	4 (13.3)
Vascular access site thrombosis	4 (13.3)	14 (46.7)
Vascular disorders	**1 (3.3)**	**6 (20.0)**
Vascular stenosis	1 (3.3)	6 (20.0)

Patients 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 patients in the analysis set, TEAE = treatment-emergent adverse event.

[3] The subjects with *Clostridium difficile* infection and coronavirus infection both died of other respectively recurrent TEAEs.

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

Outcome

The outcome of most TEAEs at study end was "recovered/resolved" (82 events) or "recovered/resolved with sequelae" (2 events); 12 TEAEs were "unresolved", 3 TEAEs were "ongoing at time of death", and for 4 TEAEs the outcome was "death".

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

3.3.1 Deaths

In total, 6 patients died over the course of the 24 months of the study due to coronavirus infection (3 patients), cardiac failure (1 patient), respiratory failure (1 patient), and hemorrhagic stroke (1 patient; T-Table 5). None of the events were assessed as related to the HAV or the procedure..

T-Table 5: Treatment-emergent adverse events leading to death after Month 12 (N = 30)

Preferred term (verbatim)	Onset day	Day of death
Cardiac failure (heart failure)	Unknown[a]	Day 338
Coronavirus infection (recurrent COVID-19 infection)	Day 331	Day 385
Coronavirus infection (severe COVID-19 infection resulting in death)	Day 344	Day 358
Respiratory failure (respiratory insufficiency)[b]	Day 672	Day 672
Hemorrhagic stroke[c]	Not recorded	Day 399
COVID-19 infection[c]	Not recorded	Day 427

Note that after Month 12 only related SAEs and events of special interest were recorded.

[a] The event started in 2020 with unknown exact start date.

[b] The event occurred during preparation for renal transplant.

[c] The event was neither related to the HAV nor an event of special interest, thus, no other data but the cause and date of death were recorded.

COVID-19 = coronavirus disease 2019, HAV = human acellular vessel, N = number of patients in the analysis set.

3.3.2 Other serious adverse events

In total, 78 serious TEAEs (TESAEs) were reported in 24 patients (T-Table 2; T-Table 6), of which 63 TESAEs in 19 patients were possibly or definitely related to the HAV. The most frequently reported TESAEs (in ≥10% of patients) were vascular access site thrombosis, anastomotic stenosis,

[4] The subject with implant site erythema also had a vascular access site hematoma.

vascular stenosis, and vascular access site pseudoaneurysm, all of which were assessed as possibly or definitely related to the HAV.

T-Table 6: Treatment-emergent serious adverse events by preferred term (N = 30)

	Number (%)[a] of patients	
Preferred term	**with TESAE(s)**	**with HAV-related[b] TESAE(s)**
Any (related) TESAE	**24 (80.0)**	**19 (63.3)**
Vascular access site thrombosis[c]	16 (53.3)	16 (53.3)
Anastomotic stenosis	10 (33.3)	10 (33.3)
Vascular stenosis	7 (23.3)	7 (23.3)
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)
Vascular access complication	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)	-
Respiratory failure	1 (3.3)	-

For patients with multiple events for one preferred term, only the strongest relationship was counted. N = 0 is shown as '-'.
[a] Percentages are based on N. [b] With possible or definite relationship.
[c] "Vascular graft thrombosis" was reworded to "vascular access site thrombosis" after the main analysis at Month 3.
HAV= human acellular vessel, N = number of patients in the analysis set, TESAE = treatment-emergent serious adverse event.

Three SAEs were life-threatening (*Clostridium difficile* infection, coronavirus infection, bacterial infection) and 4 events caused the patient's death (cardiac failure, coronavirus infection [2 events], and respiratory failure; T-Table 5, Section 3.3.1).

3.3.3 Adverse events of special interest and other significant adverse events

3.3.3.1 Overview of adverse events of special interest

In 22 patients (73.3%), AESIs were reported. The incidence of AESIs as assessed by the investigators is summarized in T-Table 7. Most frequently reported (in ≥10% of patients) were vascular access site thrombosis, anastomotic stenosis, vascular stenosis, and vascular access site pseudoaneurysm.

T-Table 7: Adverse events of special interest by preferred term (N = 30)

Preferred term	Number (%)[a] of patients	
Any AESI	**22**	**(73.3)**
Vascular access site thrombosis	17	(56.7)
Anastomotic stenosis	10	(33.3)
Vascular stenosis	7	(23.3)
Vascular access site pseudoaneurysm	5	(16.7)
Haematoma infection	1	(3.3)
Brachiocephalic vein stenosis	1	(3.3)
Vascular access complication	1	(3.3)

AESIs include all AEs for which the AESI box in the electronic case report form page was ticked. N = 0 is shown as '-'.
[a] Percentages are based on N.
AESI = adverse event of special interest, N = number of patients in the analysis set.

3.3.3.2 Analysis of adverse events of special interest

3.3.3.2.1 HAV thrombosis

34 HAV thromboses were reported in 17 patients (56.7%), corresponding to a rate of 72 thromboses per 100 patient-years of retaining secondary patency. The median time to onset of the first HAV thrombosis was 344 days (range: 2 to 687 days).

3.3.3.2.2 HAV infections

No HAV-related infections and no infections of the HAV were reported. 1 patient had coinciding hematoma infection, vascular access site pseudoaneurysm, and vascular access site thrombosis.

3.3.3.2.3 Clinically significant HAV stenoses

30 clinically significant stenoses (ie, with severity of severe or greater, or requiring a surgical or radiological intervention) were observed in 14 patients (46.7%; 17 mild, 11 moderate, and 2 severe stenoses), corresponding to a rate of 64 stenoses per 100 patient-years of retaining secondary patency. The median time to onset of the first stenosis was 346 days (range: 139 to 790 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

1 HAV anastomotic bleeding was reported in 1 patient at Day 378.

3.3.3.2.6 HAV aneurysms and pseudoaneurysms

No HAV aneurysm was observed. 5 patients (16.7%) suffered pseudoaneurysms, corresponding to a rate of 11 pseudoaneurysms per 100 patient-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 on Day 435.

3.3.3.3 TEAEs leading to abandonment or (partial) removal of the HAV

During surgery for 2 TEAEs (thrombosis and pseudoaneurysm) the HAV was partially removed due to damages noted to the HAV. In both cases, patch plasty was used for HAV repair. In 10 patients (33.3%), the HAV was abandoned due to thromboses (8 patients) or failed surgical revision to restore patency (1 patients), or both (1 patient).[5] HAVs were abandoned between Day 149 and Day 827.

3.4 Clinical laboratory evaluation

Clinical laboratory was only evaluated until Month 2 (see T-Table 1) and was 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

1 patient received a renal transplant during the study on Day 784.

[5] In 1 additional subject the HAV was abandoned after a kidney transplant. The subject was therefore censored for all secondary patency analyses.

3.5.3 Cannulation of the HAV and dialysis catheter use

Data on HAV first cannulation are provided in the main CSR and 12-month CSR addendum. In all patients, the HAV was successfully used for dialysis at least once. Overall, 11 patients (36.7%) had 1 or 2 alternative dialysis accesses created or catheters inserted post HAV implantation.

3.5.4 Examination of access site

Any problems up to and including Month 12 are reported in the main CSR and the 12-month CSR addendum. After Month 12, thrill and bruit were present in all 16 assessed patients (100%) at Month 18, and in 15 of16 patients (93.8%) at Month 24. No problems with the surgical incision or at the HAV site were reported at Month 18. At Month 24, 1 patient had a localized hematoma and another patient a non-specified abnormality. No resulting interventions were reported.

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

PRA was only assessed up until Month 12. Results are reported in the 12-month CSR addendum.

3.6 Safety summary

During long-term FU up to Month 24, 29 of 30 patients (97%) experienced TEAEs (103 events in total), and in 26 of these patients, 81 TEAEs were possibly or definitely related to the HAV. The most frequent (ie, reported in 5 or more patients) TEAEs were vascular access site thrombosis (18 patients), anastomotic stenosis (11 patients), vascular access site hematoma (8 patients), vascular stenosis (7 patients), and vascular access site pseudoaneurysm (5 patients). Most AEs were mild or moderate. 24 patients experienced 78 serious TEAEs, of which 3 events were life-threatening and 4 events resulted in death. 3 patients (of whom 2 later died of another or recurrent TEAE) had 1 life-threatening TEAE each (*Clostridium difficile* infection, coronavirus infection, bacterial sepsis). In total, 6 patients died during long-term FU. Of these, 4 patients had TEAEs that were not related to the HAV resulting in death (cardiac failure [1 patient], coronavirus infection [2 patients], and respiratory failure). Two patients died of hemorrhagic stroke and COVID-19 infection, respectively, with no further information on the TEAEs leading to death.

The AESIs HAV infections and indications of mechanical failure or weakness of the HAV, eg, spontaneous HAV ruptures and aneurysms, were not observed. AESIs reported by ≥10% of patients included vascular access site thrombosis, anastomotic stenosis, vascular stenosis, and vascular

access site pseudoaneurysm. For 2 TEAEs (thrombosis and pseudoaneurysm) the respective HAV was partially removed due to damages noted to the HAV during intervention. In both cases patch plasty was used to repair the HAV damage and the HAV was continued to be used in 1 patient. In the other patient, a dialysis catheter was placed. In 10 patients (33.3%), the HAV was abandoned due to thromboses (8 patients) or failed surgical revision to restore patency (1 patient), or both (1 patient).

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

4 Results – efficacy

4.1 Patency

At Month 24, primary patency was documented in 1 patient, primary assisted patency in 3 patients, and secondary patency in 6 patients (T-Table 8). The Kaplan-Meier probabilities to retain patency overall were 32% for primary, 44% for primary assisted, and 64% for secondary patency. The time to loss of primary and primary assisted patency ranged for both from 2 to 687 days, and time to loss of secondary patency from 149 to 586 days. Corresponding Kaplan-Meier curves are shown in T-Figure 2.

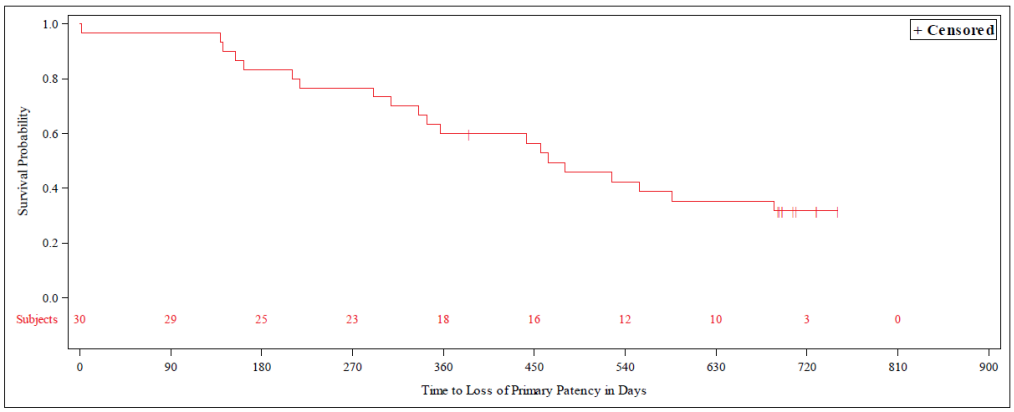
T-Table 8: Kaplan-Meier probabilities of retaining patency (N = 30)

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)	18	60.0	(40.5, 75.0)	20	66.7	(46.9, 80.5)	24	83.2	(64.2, 92.6)
Month 24 (Day 730)	1	31.8	(16.1, 48.7)	3	44.1	(25.6, 61.2)	6	64.3	(43.6, 79.0)

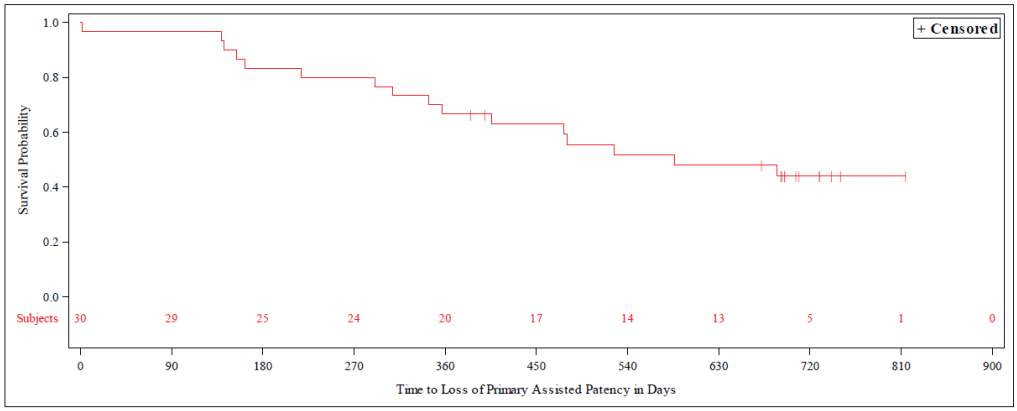
Patients who discontinued early, died, or were transplanted with the graft still patent were censored at that time point. Data of patients without loss of patency were censored at data cut-off (Month 24 visit).
CI = confidence interval, N = number of patients in the analysis set, n = number of patients at risk, Pr = probability of retaining patency.

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

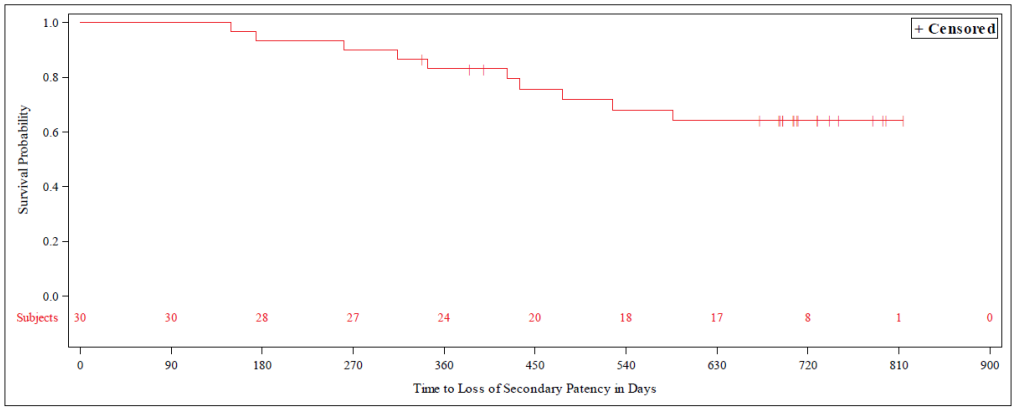
(A) Primary patency



(B) Primary assisted patency



(C) Secondary patency



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

Patency rates by sex are shown in T-Table 9. At Month 24, patency rates for women were slightly higher than that for men with 35.7% vs 27.8% for primary patency and 70.1% vs 58.3% for secondary patency, and about the same with 42.9% vs 44.6% for primary assisted patency. Corresponding Kaplan-Meier curves are shown in T-Figure 3.

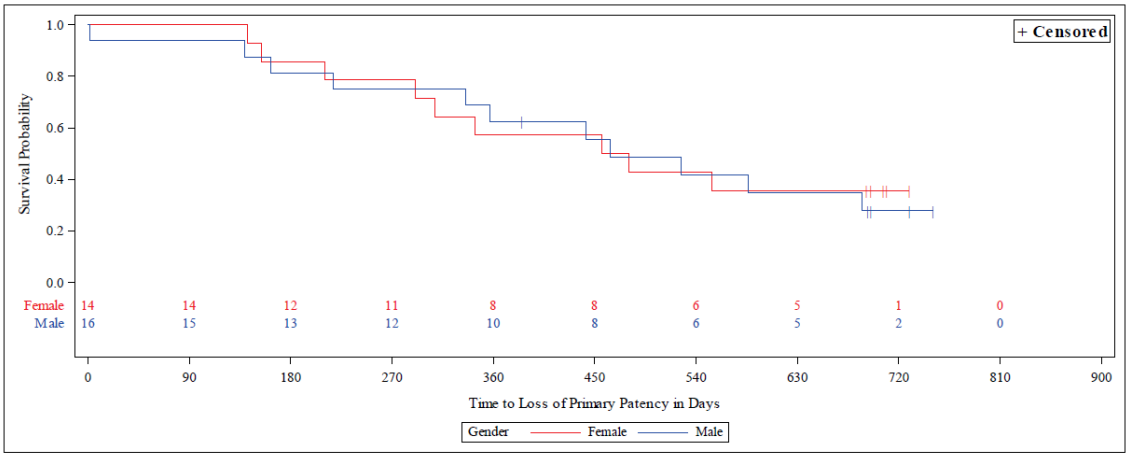
T-Table 9: Kaplan-Meier probabilities of retaining patency by sex (N = 30)

Patency by sex 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)
Month 24 (Day 730)	0	35.7	(13.0, 59.4)	1	42.9	(17.7, 66.0)	3	70.1	(38.5, 87.6)
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)	10	62.5	(34.9, 81.1)	11	68.8	(40.5, 85.6)	14	87.5	(58.6, 96.7)
Month 24 (Day 730)	1	27.8	(8.8, 51.0)	2	44.6	(18.3, 68.0)	3	58.3	(29.5, 78.8)

Patients who discontinued early, died, or were transplanted with the graft still patent were censored at that time point. Data of patients without loss of patency were censored at data cut-off (Month 24 visit).
CI = confidence interval, N = number of patients in the analysis set, n = number of patients at risk, Pr = probability of retaining patency.

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

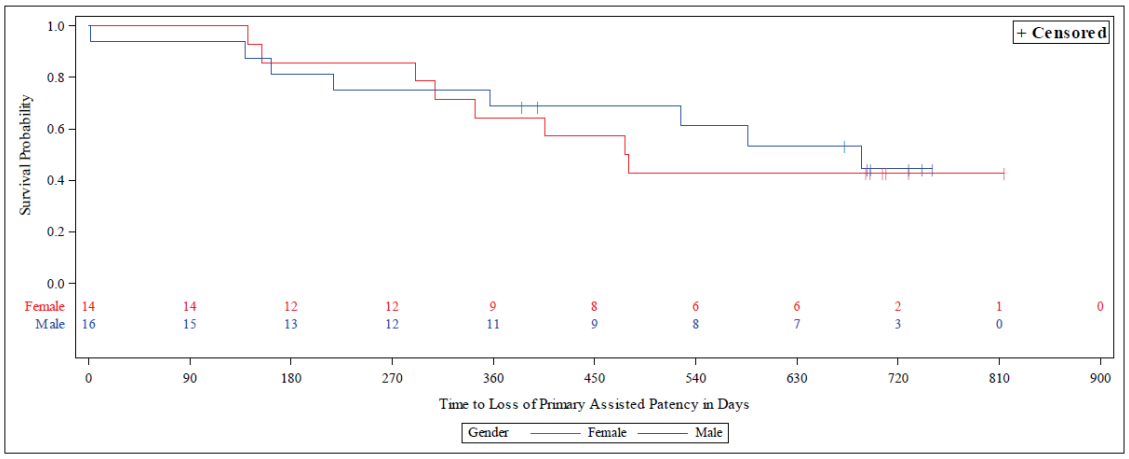
(A) Primary patency



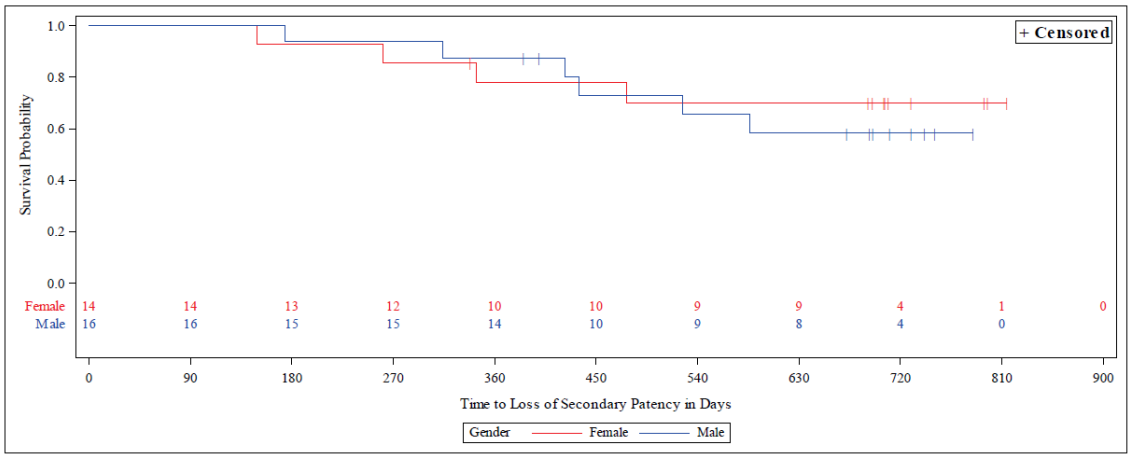
continued

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

(B) Primary assisted patency



(C) Secondary patency



Patients who discontinued early, died, or were transplanted with the graft still patent were censored at that time point. Data of patients without loss of patency were censored at data cut-off (Month 24 visit).
N = number of patients in the analysis set.

The subgroup analyses by study site showed no apparent major differences between the 2 study sites.

4.2 Other efficacy endpoints

At Month 24, 19 patients had an intervention performed to maintain patency and usability of the graft, corresponding to 93.3 successful interventions per 100 patient-years (T-Table 10). The most common (in >40% of patients) interventions were angioplasty and thrombectomy. One patient

needed a stent, and none of the patients needed a revision to maintain secondary patency. No graft ligation was performed.

T-Table 10: Interventions to maintain patency and usability of the graft (N = 30)

	Number (%)[a] of patients	Number of interventions	Successful interventions per 100 patient-years (overall)
Any intervention	**19 (63.3)**	**30**	**93.3**
Any angioplasty	14 (46.7)	27[b]	57.3
Any thrombectomy	13 (43.3)	22[c]	46.7
Partial HAV removal/excision	2 (6.7)	2	n.c.
Any stent	1 (3.3)	1	2.1
Other[d]	7 (23.3)	9[d]	n.c.

[a] Percentages are based on N.

[c] 4 patients with 2 interventions, and 1 patient with 6 interventions. [b] 4 patients with 2 interventions, 1 patient with 3 interventions, and 1 patient with 8 interventions.

[d] Other interventions included 'debridement of soft tissue due to hematoma infection', 'removal of pseudoaneurysm with reconstruction of bovine patch', 'thrombectomy with stent removal', 'angioplasty of stenosis of venous anastomosis with Dacron patch placement', 'carotid patch placement', 'placement of hemostatic stitches', 'thrombectomy and bovine patch plasty', 'thrombectomy angiojet of the HAV', and 'resection of the aneurysm with bovine pericardium patch plasty'. 1 patient with 3 interventions.

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

The HAV conduit was permanently abandoned in 10 patients[6] due to thromboses (8 patients) and failed surgical revision to restore patency (1 patients), or both (1 patient) between Day 149 and Day 827.

An overview of the blood flow rates and graft diameters determined by ultrasound during the study is given in T-Table 11. Median flow rates were comparable between Day 28 and Month 3, with a slight decrease in flow rate at Month 6 and Month 12. After Month 12, the flow rate slightly increased again until Month 24. 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 slightly smaller diameter from Month 6 to Month 24.

[6] In 1 additional subject the HAV was abandoned after a kidney transplant. The subject was therefore censored for all secondary patency analyses.

T-Table 11: 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)
	Month 18	16	1119	(588 - 2500)
	Month 24	16	1275	(0 - 2400)
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)
	Month 18	16	5.8	(5.0 - 6.5)
	Month 24	16	5.8	(5.1 – 6.5)

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

Overall, 11 patients (36.7%) had a new dialysis access inserted or catheter placed after the implantation (1 new access each in 7 patients and 2 accesses in 4 patients each). In one of these patients, the new dialysis access was used intermittently, ie, the HAV was still used as dialysis access at Month 24.

4.3 Efficacy summary

At Month 24 (Day 730), primary patency was observed in 1 patient, primary assisted patency in 3 patients, and secondary graft patency in 6 patients. The Kaplan-Meier probabilities of retaining patency at Month 24 were 32% for primary, 44% for primary assisted, and 64% for secondary patency.

At Month 24, 19 patients had at least 1 intervention performed to maintain patency and usability of the graft, corresponding to 93.3 successful interventions per 100 patient-years. One patient needed a stent, and none of the patients needed a revision to maintain secondary patency. No graft ligation was performed. In total, 11 HAV grafts were permanently abandoned between Day 149 and Day 827 due to thromboses (in 9 patients) or failed surgical revision (1 patient), or both (1 patient).

5 Conclusions

- The 24-month primary patency rate in this study was slightly higher than in previous Phase 2 studies (32% in this study versus 15% in studies CLN-PRO-V001 and CLN-PRO-V003 combined) and the secondary patency rate was slightly lower (64% in this study versus 78% in studies CLN-PRO-V001 and CLN-PRO-V003 combined)
- HAV infections and indications of mechanical failure or weakness of the HAV were not observed
- Safety results were as expected based on previous experience with the HAV, ie, AEs are in line with events reported in previous studies (CLN-PRO-V001 and CLN-PRO-V003) and described in the current version of the investigator's brochure
- Overall, these data show that the performance of HAVs in a clinical setting produced with the LUNA system does compare well to the HAVs evaluated in previous studies.