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HEALTH TECHNOLOGY BRIEFING NOVEMBER 2019

Human acellular vessel for vascular access for haemodialysis in end-stage renal disease

NIHRIO ID	8948	**NICE ID**	9222
Developer/Company	Humacyte Inc	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

The Human acellular vessel (HAV) is in clinical development to provide vascular access for haemodialysis patients with end-stage renal disease (ESRD). ESRD is a long-term irreversible condition where the kidneys do not work as well as they should as a result of chronic kidney disease. There is no cure for kidney failure and patients with this condition requires haemodialysis or a renal transplant for survival. Haemodialysis works by taking blood from the body and cleaning it through a machine to remove the toxins. Blood is filtered before being returned to the body. Vascular access is a way to reach the blood during haemodialysis.

The HAV is a bio-engineered vascular tube for dialysis access in patients with ESRD. It utilises human vascular cells to form a mechanically strong, engineered tube similar to native blood vessels. The HAV is among the first generation regenerative medicine aiming to generate artificial biological structures used to repair or replace damaged tissues and organs. If licensed the HAV will provide a treatment option for patients to use a prosthesis for vascular access in haemodialysis patients with ESRD.

PROPOSED INDICATION

The Human acellular vascular (HAV) implant for use as a vascular prosthesis for haemodialysis access in patients with end-stage renal disease (ESRD).[1,2]

TECHNOLOGY

DESCRIPTION

Human acellular vessel (HAV) implant is created from donated human smooth muscle cells placed in a tubular scaffold made of biodegradable suture material.[3] Once implanted, the HAV may be remodelled by the host (patient) to create a vascular structure more similar to native, adjacent vascular tissue.[3] Its mechanical attributes are similar to or exceed those of human mammary vein and saphenous vein.[4]

HAV implant is in clinical development as conduits for haemodialysis. In phase III clinical trials (NCT03183245; NCT02644941, HUMANITY) subjects with ESRD were randomised to receive either HAV or arteriovenous fistula (AVF)/expanded polytetrafluoroethylene (ePTFE) graft for haemodialysis access. Subjects will be followed for up to 60 months post implantation.[1,2]

INNOVATION AND/OR ADVANTAGES

The novel feature of the HAV is that it is produced in vitro using human vascular smooth muscle cells that are cultured on a bio-degradable polymer. De-cellularisation of HAV removes all living cells while retaining extracellular matrix proteins and preserving mechanical properties of the implant. Thus, HAV provides a safe and well-tolerated option which appears to be durable, withstanding repeated cannulation over periods greater than 1 year without aneurysm or structural degradation.[5]

In clinical trials, the microscopic evaluation of the HAV samples retrieved 16 weeks to 4 years after implantation in patients in phase II clinical trials providing vascular access for haemodialysis. The initial results suggest that the HAV may be an innovative advancement as a bioengineered vessel that develops characteristics of living tissue over time.[6]

Patient's cells transform the HAV into a multi-layered living tissue similar to native blood vessels and also showed evidence of ongoing cellular repair of HAV tissues that had been previously injured during cannulation with dialysis needles. These findings may suggest that the recellularised HAV is capable of self-healing.[4,6]

HAV may meet the criteria for an advanced therapy medicinal product (ATMP) classification by the European Medicines Agency (EMA). The scientific recommendation for an ATMP classification is issued by the EMA's Committee for Advanced Therapies (CAT).[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

HAV does not currently have Marketing Authorisation in the EU/UK for any indication.

HAV is also in phase II for clinical development for vascular trauma and phase III clinical development for peripheral artery disease.[8]

The HAV was designated Regenerative Medicine Advanced Therapy for vascular access for haemodialysis by FDA in March 2017.[9]

PATIENT GROUP

DISEASE BACKGROUND

Chronic kidney disease (CKD) is a long-term irreversible and typically progressive condition where the kidneys do not work as well as they should. CKD can be caused by many diseases but it is often found in patients who also have diabetes and high blood pressure.[10,11]CKD is classified in five stages, according to the level of kidney damage and the ability of the kidneys to filter blood.[12]

ESRD is the last stage of long-term (chronic) kidney disease.[13,14] This means kidneys are only functioning at 10-15% of their normal capacity. When kidney function is this low, they cannot effectively remove waste or excess fluid from the blood. Kidneys are also responsible for other functions that support the body, such as balancing electrolytes and producing certain hormones.[14] When CKD develops into ESRD, the body is unable to excrete waste products excess water, acid and salts resulting in increasing symptoms and eventually death.[15] When end renal stage is reached haemodialysis or kidney transplant is necessary to stay alive.[14,15]

Haemodialysis works by taking blood from the body and cleaning it through a machine to remove the toxins. Blood is filtered before being returned to the body. Toxins move from the blood into dialysis fluid and the dialysis fluid is then drained.[16] The arteriovenous (AV) fistula, AV graft and venous catheter provide permanent vascular access for haemodialysis. The main benefit of AV grafts is that they do not require maturation, as AV fistulas do, and that they can be used for haemodialysis in as little as 24 hours after creation depending upon the type of graft that is being used.[17]

Vascular access makes life-saving haemodialysis treatments possible for kidney failure that uses a machine to send the patient's blood through a filter outside the body. The access is a surgically created vein used to remove and return blood during haemodialysis.[18]

Vascular access complications are of great burden in the haemodialysis population and can cause problems that may require further treatment or surgery.[18,19] The most common problems associated with vascular access include access infection and low blood flow due to blood clotting in the access.[18]

CLINICAL NEED AND BURDEN OF DISEASE

Moderate to severe CKD affects approximately 5.5% of adults and is more common in older people.[20]

The CKD prevalence model provides estimates of total CKD prevalence for adults aged 16 and over in England. The model was developed using data from the Health Survey for England (HSE) – 2009 and 2010 and the 2011 Census. It is expected that 2.6 million people aged 16 years and older in England have CKD stage 3-5. This is equal to 6.1% of the population of this age group. CKD stage 3-5 prevalence is higher in women than in men, 7.4% versus 4.7%. There is a clear association between increasing age and higher CKD stage 3-5 prevalence; with 1.9% of people aged 64 and underestimated to have CKD stage 3-5, 13.5% of people aged 65-74 and 32.7% of people aged 75 and over.[21]

In England, each year about 5,800 people start treatment for kidney failure and about four in 10 are treated with haemodialysis while one in 10 is treated with peritoneal dialysis.[22] Around

30,000 patients are on dialysis and approximately 3,000 kidney transplants take place every year in the UK.[23]

In England, in 2018-19 there were 31,236 hospital admissions, 46,773 Finished Consultant Episodes (FCE), and 17,149 day-cases and 96,811 FCE-bed days in England for CKD stage 5 (ICD 10 Code: N18.5).[24]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There are limited treatment options for patients with ESRD which include haemodialysis peritoneal dialysis or a kidney transplant.[25,26] Based on the medical conditions and patients opt to choose one or more of these treatments.[25] In most cases, patients have haemodialysis or peritoneal dialysis before a kidney transplant.[26]

Haemodialysis uses dialysis to clean blood. Blood is taken through a tube from a vein either an arm or neck. The dialysis machine removes excess waste products and water through a special filter (dialyser) and cleaned blood is returned through a tube into the vein.[26] The majority of haemodialysis is performed in a dialysis centre, where patients spend 3–5 hours on the machine 2–4 times a week.[25,27]

CURRENT TREATMENT OPTIONS

Clinical practice guideline from the UK Renal Association recommend that all patients with ESRD who commence haemodialysis or are on long-term haemodialysis should dialyse with an arteriovenous fistula as first choice, an arteriovenous graft as the second choice, a tunnelled venous catheter as third choice and a non-tunnelled temporary catheter as an option of necessity.[28]

PLACE OF TECHNOLOGY

If licensed, the HAV will offer a treatment option for use as a vascular prosthesis for haemodialysis access in patients with ESRD.

CLINICAL TRIAL INFORMATION

Trial	NCT03183245, CLN-PRO-V007; **adults ≥ 18 yrs; HAV vs arteriovenous fistula (AVF); phase III**
Sponsor	Humacyte, Inc
Status	Ongoing
Source of Information	Trial registry[1], manufacturer [a]
Location	USA
Design	Randomised, parallel-assignment, open-label
Participants	n= 240 (planned); aged ≥ 18 yrs; ESRD, receiving haemodialysis via dialysis catheter (DC) and are suitable for the creation of an AVF or implantation of AVG for haemodialysis access; patients who plan to undergo haemodialysis at a dialysis unit; haemoglobin ≥8 g/dL and platelet count ≥100,000 /mm^3

[a] Information provided by Humacyte Inc

Schedule	Pts randomised to one of two arms • Experimental: The HAV is a tissue-engineered vascular conduit (6mm diameter) for haemodialysis access in patients with ESRD. It will be surgically implanted in the forearm or upper arm on study day 0 • Active comparator: The comparator is an AVF created in the forearm or upper arm on study day 0
Follow-up	60 mths
Primary Outcomes	• Proportion of subjects with functional patency at 6 mths post study access (SA) creation [Time frame: 6 mths post SA creation] • Proportion of subjects with secondary patency of SA at 12 mths post SA creation [Time frame:12 mths post SA creation]
Secondary Outcomes	• Time to loss of secondary patency (abandonment). [Time frame: 12, 24, and 60 mths post SA creation] • Incidence rate of haemodialysis access related interventions over the period from SA creation until SA abandonment or 12 mths post SA creation [Time frame: 12 mths post SA creation] • Incidence rate of infections related to any haemodialysis access in situ over the period from SA creation until 12 mths post SA creation, irrespective of SA abandonment. [Time frame: 12 mths post SA creation] • Proportion of subjects with unassisted functional patency at 6 mths post SA creation. [Time frame: 6 mths post SA creation] • Incidence rate of haemodialysis access-related interventions over the period from SA creation until SA abandonment or the conclusion of the suitability ascertainment period (6 mths) [Time frame: 6 mths post SA creation] • Time to loss of primary unassisted patency [Time frame: 12, 24, and 60 mths post SA creation] • Proportion of haemodialysis sessions completed via DC (1 or 2 lines) over the period from SA creation until 12 mths post SA creation, irrespective of SA abandonment. [Time frame: 12 mths post SA creation] • Number of days with DC in situ "catheter contact time" over the period from SA creation until 12 mths post SA creation, irrespective of SA abandonment [Time frame: 12 mths post SA creation] • Histopathological remodeling of HAV and AVF - based on histological examination of SA samples explanted for clinical reasons[Time frame: 12, 24, and 60 mths post SA creation] • Incidence rate of haemodialysis access-related infections over the period from SA creation until SA abandonment. [Time frame: 12, 24, and 60 mths post SA creation] • Incidence rate of clinically significant aneurysm or pseudoaneurysm over the period from SA creation until SA abandonment [Time frame: 12, 24, and 60 mths post SA creation] • Incidence rate of SA site infections (CDC definition) over the period from SA creation until SA abandonment. [Time frame: 12, 24, and 60 mths post SA creation] • Frequency and severity of AEs. [Time frame: 12, 24, and 60 mths post SA creation]
Key Results	-

Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as Q2 2021. Estimated study completion date reported as Q2 2024.

Trial	**HUMANITY, NCT02644941, CLN-PRO-V006, EudraCT-2015-003261-28; adults ≥ 18 yrs; HAV vs ePTFE; phase III**
Sponsor	Humacyte, Inc
Status	Ongoing
Source of Information	Trial registry[2,29]
Location	EU (incl UK), USA and Israel
Design	Randomised, parallel-assignment, open-label
Participants	n=355; aged ≥ 18 yrs; ESRD who are not, or who are no longer, candidates for creation of an autologous AVF and therefore need placement of an AVG in the arm (upper- or forearm) to start or maintain haemodialysis therapy; either on haemodialysis or expected to start in 12 wks; haemoglobin ≥8 g/dL and platelet count ≥100,000 cells/mm^3 prior to day 0 (within 35 days)
Schedule	Pts randomised to one of two arms • Experimental: The HAV is a tissue-engineered vascular conduit (6mm diameter) for haemodialysis access in pts with ESRD. It will be surgically implanted in the forearm or upper arm on study day 0 • Active Comparator: The comparator (one of two commercially available 6mm ePTFE grafts) will be surgically implanted in the forearm or upper arm on study day 0
Follow-up	60 mths
Primary outcomes	• Time to loss of secondary patency from implantation [Time frame: 18 mths post-implantation]
Secondary outcomes	• Time to loss of secondary patency from implantation [Time frame: 12, 24 & 60 mths post-implantation] • Time to loss of primary patency from implantation [Time frame: 12,18, 24, & 60 mths post-implantation] • Access-related infections [Time frame: 12, 18, 24, & 60 mths post-implantation] • Rate of interventions required to achieve/maintain Secondary Patency [Time frame: 12, 18, 24, & 60 mths post-implantation] • Time to loss of primary assisted patency from implantation [Time frame: 12, 18, 24, & 60 mths post-implantation] • Histopathological remodeling of any study conduit [Time frame: Up to 60 mths post-implantation] • The efficiency of dialysis as assessed by spKt/Vurea (subset of subjects) [Time frame: 12, 18 & 24 mths post-implantation] • Frequency and severity of AEs [Time frame: 12, 18, & 24 mths post-implantation] • True aneurysm formation (conduit lumen diameter >9mm) [Time frame: 12, 18, 24, & 60 mths post-implantation] • Pseudoaneurysm formation [Time frame: 12, 18, 24, & 60 mths post-implantation]

	• Study conduit rupture [Time frame: 12, 18, 24, & 60 mths post-implantation] Anastomotic bleeding or rupture [Time frame: 12, 18, 24, & 60 mths post-implantation]
Key results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as September 2022. Estimated study completion date reported as September 2022.

ESTIMATED COST

The cost of the HAV is not known yet.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE interventional procedure guidance. Laparoscopic insertion of peritoneal dialysis catheter (IPG 208). February 2018.
- NICE quality standard. Renal replacement therapy service for adults (QS72). October 2018.
- NICE diagnostic guidance. Multiple frequency bioimpedance devices to guide fluid management in people with chronic kidney disease having dialysis (DG29). June 2017.
- NICE clinical guideline. Chronic kidney disease (stage 5): peritoneal dialysis (CG125). July 2011.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Commissioning Policy. Dialysis away from base. A06/p/a.

OTHER GUIDANCE

- Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of chronic kidney disease: A national clinical guideline (SIGN 103). June 2008.[30]

ADDITIONAL INFORMATION

Humancyte did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.