NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Sirolimus-eluting collagen implant for preventing vascular access failure in end stage renal disease patients undergoing haemodialysis

Company/Developer	Vascular Therapies Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 11914	NICE TSID: 9147	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Sirolimus-eluting collagen implant is in clinical development for prevention of arteriovenous (AV) vascular access dysfunction in patients with end stage renal disease (ESRD) who are undergoing haemodialysis. ESRD, also known as stage 5 chronic kidney disease (CKD) require either a kidney transplant or dialysis to remove excess fluid and waste products from the blood when their kidneys no longer work properly. Haemodialysis is a procedure where the blood is taken from the patient, filtered and cleaned by a dialysis machine, and then returned to the patient. In order to facilitate haemodialysis, surgery to connect an artery and vein is required for vascular access. However, vascular access failure or dysfunction is common and is an important unmet medical need.

Sirolimus eluting collagen implant consists of the active medicinal product sirolimus, which is contained within a collagen membrane. It is inserted during the time of AV vascular access surgery. Following insertion of the implant, sirolimus is released and interacts with mammalian target of rapamycin (a type of protein). This helps to prevent blood vessels from narrowing and blocking which is a common cause of vascular access failure. If licenced, sirolimus-eluting collagen implant will offer an additional treatment option for ESRD patients who are undergoing haemodialysis.

Proposed Indication

Patients with end stage renal disease (ESRD) who are undergoing vascular access surgery for haemodialysis.[1,2]

Technology

Description

Sirolimus-eluting collagen implant (Sirogen) consists of a medicinal product called sirolimus which is contained within a collagen membrane. It is delivered intraoperatively as a single-dose prophylactic at the time of AV fistula surgery to enable a vein to mature and become useable for haemodialysis. Once implanted, sirolimus is released from the collagen membrane and combines with the mammalian target of rapamycin (mTOR) to suppress cell proliferation.[3,4] This suppression of excessive cell proliferation can reduce the risk of neointimal hyperplasia and flow-limiting stenosis inside the vein that cause failure or dysfunction of the AV vascular access for haemodialysis.[4]

In the phase III clinical trial (ACCESS2, NCT05425056), participants receive sirolimus-eluting collagen implant at and around the site of the anastomosis of an AV fistula immediately following completion of a successful AV fistula surgery.[2]

Key Innovation

There is a need for new therapies to prevent vascular access dysfunction, which contributes substantially to haemodialysis patients morbidity and mortality, requires corrective procedures and places a high demand on health care costs.[5] The sirolimus-eluting collagen implant delivers sirolimus to the walls of blood vessels reducing the risk of them narrowing or blocking through preventing the proliferation (growth) of muscle cells. By preventing the narrowing or blockage of blood vessels, the implant enables maturation of the blood vessel so it can be used for haemodialysis.[4,6] Clinical proof to support the antiproliferative action comes from the extensive experience of sirolimus-eluting coronary stents. In comparison to other cytotoxic antiproliferative therapeutics which have a very narrow margin of safety (which, if breeched, can result in vascular necrosis), sirolimus eluting collagen implant is a cytostatic with a wide therapeutic window and negligible vascular toxicity.[4]

If licenced, sirolimus-eluting collagen implant will be the first medicinal product recommended by NICE for prevention of AV access failure amongst ESRD patients undergoing vascular access surgery for haemodialysis.

Regulatory & Development Status

Sirolimus-eluting collagen implant does not currently have marketing authorisation in the EU/UK for any indication.

Sirolimus-eluting collagen implant has been awarded the following regulatory designations:

- EMA orphan designation for the prevention of arteriovenous access dysfunction in haemodialysis patients (December 2013).[6]
- US FDA orphan designation for prevention of AV fistula or AV graft failure in patients with ESRD receiving or preparing for haemodialysis (October 2012).[7]

Sirolimus-eluting collagen implant is not currently in phase II or III development for any other indications.[8]

Patient Group

Disease Area and Clinical Need

End stage renal disease (ESRD), which is also referred to as stage 5 chronic kidney disease (CKD), occurs when a patient's kidney function is reduced to 15% or less. At this stage the kidneys are no longer able to filter blood effectively so a kidney transplant or dialysis is required. There are two main types of dialysis: peritoneal dialysis and haemodialysis. Haemodialysis is a procedure where a dialysis machine performs some of the work of the kidneys by filtering harmful wastes, salts and fluid from the blood.[9] Vascular access surgery is required before haemodialysis to allow blood to travel from the patient to the dialysis machine.[10] Vascular access surgery options include: AV fistula creation, where an artery and vein are connected together in the arm; AV graft, where a synthetic tube connects an artery and vein in the arm; or placement of a central venous catheter in the neck.[10,11] AV access dysfunction occurs when the blood vessels used for haemodialysis narrow and become blocked so haemodialysis cannot be performed.[6] The major causes of haemodialysis vascular access dysfunction are initial failure of the AV fistula to mature and venous stenosis as a result of neointimal hyperplasia.[12,13]

In the UK there are around 68,000 patients with ESRD.[14] In England, (2021-22), there were 46,910 finished consultant episodes (FCE) and 36,100 admissions for stage 5 CKD (ICD-10 code n18.5), which resulted in 18,970 day cases and 94,207 FCE bed days. In the same year, there were 42,918 FCE and 22,543 admissions for haemodialysis (OPCS-4 code x40.3) which resulted in 6,451 day cases and 162,005 FCE bed days.[15] Vascular access dysfunction is the leading cause of dialysis related morbidity and is associated with 15% to 25% of hospital stays amongst patients with ESRD. It is estimated that it occurs in 16% to 30% of patients within 3 years after the creation of the access.[16]

Recommended Treatment Options

Clinical practice guideline from the UK Renal Association recommends that all patients with ESRD who are undergoing haemodialysis should dialyse with an AV fistula as the first choice treatment option to obtain the vascular access necessary for haemodialysis. If an AV fistula is not suitable, the second choice would be AV graft, followed by a venous catheter.[17]

Currently there are no pharmacological treatments recommended by National Institute for Health and Care Excellence (NICE) to prevent AV access failure in haemodialysis.[18]

Clinical Trial Information

Trial	**ACCESS, NCT02513303;** A Phase 3, Randomized, Multicenter, Single-blind, Controlled Study Evaluating Arteriovenous Fistula Outcomes With and Without a Perivascular Sirolimus-Eluting Collagen Implant **Phase III** – Completed **Location(s):** United States **Actual study completion date:** June 2021
Trial Design	Randomised, single-blind, triple masked, parallel assignment
Population	N=269 (actual); adults aged 18 years and older; currently on haemodialysis for ≤ 12 months or expected to initiate haemodialysis within approximately 6 months of the creation of the AV fistula;

Intervention(s)	Sirolimus-eluting collagen implant placed at and around the site of the anastomosis of an AV fistula, immediately following completion of a successful AV fistula surgery
Comparator(s)	AV fistula surgery without sirolimus-eluting collagen implant
Outcome(s)	Primary outcome measure: Fistula suitability for dialysis at 6 months [Time frame: 6 months] See trial record for full list of outcome measures
Results (efficacy)	The primary endpoint of fistula suitability for dialysis at 6 months was not achieved. Exploratory subgroup analysis showed that despite randomisation, the treatment group had a significantly higher proportion of patient aged 65 years and older. A post hoc analysis of the risk-differentiated data using an age cut of off of 65 years showed promising results for ESRD in patients aged 65 years and older who required an AV fistula for dialysis including: improved overall AV fistula maturation; improved radiocephalic AV fistula maturation; improved suitability for dialysis at 12 months; and improved secondary patency.[4,19]
Results (safety)	There were no unexpected adverse events, confirming the overall favourable safety profile of sirolimus-eluting collagen implant.[19]

Trial	**ACCESS 2,** NCT05425056**;** A Phase 3, Prospective, Randomized, Multicenter, Single-blind, Controlled Study Evaluating Arteriovenous Fistula Outcomes With and Without a Perivascular Sirolimus Eluting Collagen Implant **Phase III** - Recruiting **Location(s):** UK and US **Primary completion date**: March 2024
Trial Design	Randomised, triple masked, single-blind, parallel assignment
Population	N=120 (planned); adults aged 65 years and older; currently on haemodialysis for ≤12 months; successful creation of a single stage radiocephalic end to side fistula
Intervention(s)	Sirolimus eluting collagen implant placed at and around the site of anastomosis of an AV fistula, immediately following completion of a successful AV fistula surgery
Comparator(s)	AV fistula surgery without sirolimus-eluting collagen implant
Outcome(s)	Primary outcome measure: Clinical fistula maturation [Time frame: 6 months] See trial record for full list of outcome measures
Results (efficacy)	-
Results (safety)	-

Estimated Cost
The estimated cost of sirolimus-eluting collagen implant is not yet known.

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Chronic kidney disease: assessment and management (NG203). November 2021. Updated: November 2021.
- NICE clinical guideline. Renal replacement therapy and conservative management (NG107). October 2018.
- NICE quality standard. Renal replacement therapy services for adults (QS72). November 2014. Updated: October 2018.
- NICE interventional procedure guidance in development. Endovascular forearm arteriovenous fistula creation for haemodialysis access (GID-IPG10186). Expected date of issue to be confirmed.
- NICE interventional procedures guidance. Percutaneous endovascular forearm arteriovenous fistula creation for haemodialysis access (IPG710). October 2021.
- NICE diagnostic guidance. Multiple frequency bioimpedance devices to guide fluid management in people with chronic kidney disease having dialysis (DG29). June 2017.

NHS England (Policy/Commissioning) Guidance

- NHS England. Commissioning policy: Dialysis Away from Base. February 2016.

Other Guidance

- National Kidney Foundation. Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines for vascular access: 2019 update. 2020.[20]
- UK Renal Association. Clinical practice guideline: Vascular access for haemodialysis. 2015.[17]

Additional Information

Vascular Therapies Inc 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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