TITLE PAGE

Protocol Title	BEACH Trial: Bovine Early Access, Compatibility and Hemostasis Post-Market Trial to Evaluate the Safety and Effectiveness of Early Access in Patients Who Require an Arteriovenous Conduit for Hemodialysis using the Artegraft® Collagen Vascular Graft™
Short Title	BEACH Trial: Bovine Early Access, Compatibility and Hemostasis Trial
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Sponsor Name	Artegraft, Inc.
Legal Registered Address	206 North Center Drive North Brunswick, NJ, USA 08902
Phone	Phone: 800-631-5264
Primary Investigator	Mahmoud Malas, MD, Chief, Vascular and Endovascular Surgery University of California, San Diego
Medical Monitor	Mark Tulchinskiy, MD, MBA Senior Medical Director IQVIA BioTech, Morrisville, North Carolina

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Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, applicable independent institutional review boards, and regulatory agencies. The contents of this document shall not be disclosed to others without written authorization from Artegraft, Inc. (or others, as applicable), unless it is necessary to obtain informed consent from potential study participants.

Protocol Approval

Sponsor Approval: Richard A. Gibson, President and Chief Executive Officer

Signed: _____ Date: 6/24/19

Sponsor Clinical Affairs Approval: Steven Weinberg, PhD, Vice President, Clinical Affairs

Signed: _____ Date: 6/21/19

Sponsor Signatory Statement of Compliance

This trial will be conducted in compliance with the protocol and the following regulatory requirements:

- Declaration of Helsinki adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, as last amended by the World Medical Assembly in 2008
- Applicable sections of United States Food and Drug Administration (FDA) Code of Federal Regulations (CFR), including:
  - 21 CFR Part 50, Protection of Human Patients
  - 21 CFR Part 54, Financial Disclosure by Clinical Investigators
  - 21 CFR Part 56, Institutional Review Boards
  - 21 CFR Part 812, Investigational Device Exemption Application
  - 21 CFR Part 803, Medical Device Reporting

The conduct of the trial will be approved by the appropriate Institutional Review Board (IRB) of the respective investigational site(s) and by the U.S. FDA.

Sponsor Representative: Steven Weinberg, PhD, Vice President, Clinical Affairs

Signed: _____ Date: 6/20/19

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1.0 PROTOCOL SUMMARY

Clinical Investigation Title	BEACH Trial: Bovine Early Access, Compatibility, and Hemostasis Trial Study to Evaluate the Safety and Effectiveness of Early Access in Patients Who Require an Arteriovenous Conduit for Hemodialysis using the Artegraft® Collagen Vascular Graft™
Short Title	Bovine Early Access, Compatibility, and Hemostasis (BEACH) Trial
Investigational Device	Artegraft® Collagen Vascular Graft™ (Artegraft)
Intended Use	The intended use and design of the Artegraft is unchanged. The following paragraph is from the Artegraft IFU: "The Artegraft is intended for use distal to the aorta as a segmental arterial replacement, as an arterial bypass, as an arteriovenous shunt where more conventional methods have proven inadequate, or as an arterial patch graft."
Study Objective	The objective of the BEACH Trial is to demonstrate that early access of Artegraft is associated with acceptable rates of successful early access, and acceptable rates of a composite of adverse events, to support a modification of existing device labeling stating that Artegraft is capable of cannulation within 72 hours post implantation.
Study Population	Patients with end-stage renal disease (ESRD) who require hemodialysis and are suitable for an arteriovenous graft (AVG) for hemodialysis.
Study Design	Prospective, multi-center randomized, open-label, treatment trial Eligible patients will be implanted with the Artegraft. After successful implant, Patients will be randomly assigned in a 2:1 ratio to early access [within 72 hours post implantation] or late access [>/= 10 days], of the Artegraft device. Day 0 is the date of first successful cannulation of the Artegraft for each patient. Patients with early access will be followed for 6 months post implantation. Patients with late access will be followed to at least 30 days after first access [30 days post Day 0]. The late access group will also be assessed for patency at 6 months through a telephone interview or office visit to provide a more robust data set.
Patient Number	A total of 50 patients will be randomized to early access, successfully provided early cannulation within 72 hours, and will be followed to 6 months, to provide the data required for submission to the FDA. A 12month assessment for unexpected complications will also be obtained for early access subjects. Patients randomized to the early access group who are not cannulated in the <72-hour period will be followed as a late-access subject

	for 30 days after first cannulation. It is estimated that up to 10 additional patients may fall into this category. A total of 25 patients will be randomized to late access, cannulated at 10 days or later after implant and followed for at least 30 days after first cannulation [Day 0] to assess perioperative major adverse clinical events (MACE) rates and patency data. The late access group will also be assessed for patency at 6 months through a telephone interview or office visit to provide a more robust data set
Intervention Description	Patients will be implanted with the Artegraft, for vascular cannulation for hemodialysis, using standard vascular techniques, according to the Instructions for Use.
Number of Investigators and Study Centers	Up to five (5) investigational sites are expected to participate in the trial.
Study Duration	The enrollment goal is ≥3 patients per site, per month. The anticipated enrollment period is 6 months; the patient enrollment duration for early-access patients is a minimum of 6 months, and total study duration is expected to be 12 months. The follow-up period on the early access patients will be 6 months and 30 days on the late access patients. In addition, a follow-up telephone call, based on a questionnaire, will be made to the early access patients and/or dialysis centers to determine if any unexpected complications had occurred during the 6-12-month period. For this reason, all patients will be consented to 12 months. The late access group will also be assessed for patency at 6 months through a telephone interview or office visit to provide a more robust data set.
Primary Effectiveness Endpoint	Early access success, defined by three cannulations, the first one started within 72 hours after implantation, all with minimum dialysis flow rates of 250 ml/min pump flow rate, with a minimum 17-gauge needle.
Primary Safety Endpoint	A composite of major adverse clinical events (MACE) including perigraft infection, hemorrhage / hematoma, thrombosis, and pseudoaneurysm within 30 days after first cannulation [Day 0] in the early-access and late-access groups.
Secondary Effectiveness Endpoints	Patency (Primary, Assisted Primary, and Secondary) at 30 days after first successful cannulation [Day 0], and at 12 and 6 months after implantation in the early-access group and at 30 days post-Day 0 in the late-access group. The late access group will also be assessed for patency at 6 months through a telephone interview or office visit to provide a more robust data set.

Secondary Safety Endpoint (for information only)	All adverse events will be collected in the early-access group [to 6 months] and the late-access group [to 30 days post Day 0] and summarized by unique event, seriousness, and relationship to device or procedure.
Secondary Catheter Removal Endpoint (for information only)	The number of days from graft implant or fistula revision to catheter removal shall be recorded.
Safety Monitoring	The principal or co-investigator at each site will perform the initial characterization of each serious event. The independent assessor will adjudicate each reported serious event for seriousness and relationship to device or procedure.
Timing of Cannulation	The first day of cannulation will be defined as Day 0. Any patients in the late group that require cannulation prior to the 10-day cannulation period will receive Standard of Care treatment. Dialysis will be initiated using an existing dialysis catheter or after placement of a new dialysis catheter. Hemodialysis with Artegraft will commence after the 10-day waiting period. Any patients that are in the early access group that are not cannulated within 72 hours shall still be followed for 30 days after their first cannulation. It is estimated that up to 10 additional patients may fall into this category. These patients will be treated using a dialysis catheter until their first cannulation after 10 days. They shall be replaced by additional patients using the randomization plan until the 50-patient number is reached.
Data for Information Only	Time to catheter removal [from Artegraft implantation]
Inclusion Criteria	1. Male or Female, 18 years or older 2. Diagnosis of End Stage Renal Disease (ESRD) and require vascular cannulation for hemodialysis 3. Native [autogenous tissue] AV fistula creation or cannulation is not indicated or non-viable [disadvantaged veins] 4. Requiring repair of an existing fistula or conduit, but only if using Artegraft as an interposition placement and the Artegraft is cannulated [not the fistula]. Graft must be placed in a fresh subcutaneous tunnel. Thigh loop grafts will not be used. 5. Able to accommodate vascular graft placement in the upper extremity (i.e., forearm, or upper arm) 6. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) 7. Able and willing to comply with the study protocol

	8. Agrees to initiate and maintain hemodialysis treatments 9. Life expectancy is > 1 year based on physician assessment
Exclusion Criteria	Patients are excluded from the trial if any of the following criteria apply: 1. High grade central venous stenosis/occlusion 2. Breast-feeding, pregnant or planning pregnancy within next 12 months. 3. Non-resolved infected existing grafts 4. Documented sepsis/bacteremia by blood culture within 4 weeks of implantation. 5. History of non-controlled immunodeficiency syndrome, including AIDS/HIV; Active clinically significant immune-mediated disease, not controlled by low-dose maintenance immunosuppression. The diagnosis of HIV alone, provided adequately treated, is not a contraindication for enrollment. 6. Severe liver dysfunction and/or coagulation or bleeding disorders. 7. Elevated platelet count > 1 million cells/mm3 8. History of heparin-induced thrombocytopenia syndrome (HIT) 9. Documented hypercoagulable state 10. Currently participating in another investigational drug or device study which may clinically interfere with any endpoints of this trial 11. Known hypersensitivity or contraindication to device materials or procedural medications that cannot be adequately managed medically 12. History or evidence of severe cardiac disease (NYHA Functional Class III or IV), myocardial infarction within 6 months of enrollment, ventricular tachyarrhythmias requiring continuing treatment, or unstable angina, uncontrolled CHF 13. History or evidence of severe peripheral arterial disease in the extremity selected for implant (i.e. arterial inflow insufficient to support hemodialysis) 14. History of cancer with active disease or treatment within the previous year, except for non-invasive basal or squamous cell carcinoma of the skin 15. Bleeding diathesis, other than that associated with ESRD 16. Scheduled renal transplant within 6 months 17. Patients who require chronic anticoagulation except for antiplatelet therapy. Patients currently receiving or who have received within the last month direct thrombin inhibitors, factor Xa inhibitors, or vitamin K antagonists should not be included in the study.

Data Populations	All patients who receive an Artegraft implant will be included in the safety and performance analyses for the device. The early-access group is composed of the 50 patients that are enrolled, implanted with the Artegraft, successfully provided the first cannulation within 72 hours, and are followed to 6 months. This early-access population will be used to assess Primary, Assisted Primary, and Secondary Patency at 4, 12, and 26 weeks. This early-access population also will be used to assess perioperative major adverse clinical events (MACE) rates, and all adverse events to 26 weeks. The late-access group is composed of 25 patients that are enrolled, implanted with the Artegraft, that are first accessed at >/= 10 days, and that are followed to 30 days post Day 0. This group will be used to assess perioperative major adverse clinical events (MACE) rates and primary, assisted primary, and secondary patency, at 30 days post Day 0. The late access group will also be assessed for patency at 6 months through a telephone interview or office visit to provide a more robust data set.

Table 1a: Schedule of Assessments (SoA) Early Access Patients

Procedure	Screening Day -45 to Day of Surgery	Day 0 [1st successful cannulation] (May occur on day of surgery)	Day 1 – 17 Days post Day 0	Day 30 +/- 3 days post Day 0	12 weeks +/- 7 days post day 0	6 Months +/- 7 days post day 0	12 Months +/- 14 days post day 0* Extended Follow-up
Eligibility (inclusion/exclusion)	X						
Informed Consent	X						
Medical History	X						
Prior and concomitant medication	X		X	X	X	X	
Physical Exam	X		X	X	X	X	
12-Lead ECG, when medically indicated	X						
Vessel mapping (if not done within 8 weeks)	X						
Pregnancy test: serum (Women of child-bearing potential only; to be assessed within 7 days of implant)	X						
Hematology and coagulation lab test	X						
Surgical implant of Artegraft	X						
Documentation of surgical procedure	X						
Assessment of wound healing		X	X	X	X	X	
Graft Patency Assessment	X	X	X	X	X	X	X
Adverse event assessment	X	X	X	X	X	X	X+
Medical Device malfunctions	X	X	X	X	X	X	
Documentation of graft interventions	X	X	X	X	X	X	
Use of Dialysis Catheter		X	X	X	X	X	

These patients will be having dialysis every few days – assessments should be the same or similar at each post-implant visit.

* Extended follow-up will be assessed for patency and AEs only via a telephone follow-up or office visit

+ AEs between 6 months and 12 months.

Table 2b: Schedule of Assessments (SoA) Late Access and Early Access Drop-outs

Procedure	**Screening Day -45 to Day of Surgery**	**Day 0 [1st successful cannulation] (May occur on day of surgery)**	**Day 1 – 17 Days post Day 0**	**Day 30 +/- 3 days post Day 0**	**6 Months +/- 7 days post day 0* Extended Duration Follow-up**
Eligibility (inclusion/exclusion)	X				
Informed Consent	X				
Medical History	X				
Prior and concomitant medication	X		X	X	
Physical Exam	X		X	X	
12-Lead ECG, when medically indicated	X				
Vessel mapping (if not done within 8 weeks)	X				
Pregnancy test: serum (Women of child-bearing potential only; to be assessed within 7 days of implant)	X				
Hematology and coagulation lab test	X				
Surgical implant of Artegraft	X				
Documentation of surgical procedure	X				
Assessment of wound healing		X	X	X	
Graft Patency Assessment	X	X	X	X	X
Adverse event assessment	X	X	X	X	X +
Medical Device malfunctions	X	X	X	X	
Documentation of graft interventions	X	X	X	X	
Use of Dialysis Catheter		X	X	X	

These patients will be having dialysis every few days – assessments should be the same or similar at each post-implant visit.

** Late access patients will be assessed for patency and AEs only via a telephone follow-up or office visit

+ AEs during time between 1 month and 6 months

2.0 INTRODUCTION

2.1 Clinical Background

Chronic kidney disease (CKD) is a major health problem that affects approximately 26 million Americans.[1] Many of those suffering CKD will progress to develop end stage renal disease (ESRD) and require lifelong hemodialysis (HD) to filter wastes from their blood. There are nearly 2.5 million patients who receive HD worldwide, and this population is growing at a rate of 8% per year.[2] This projects that the worldwide HD population to reach approximately 3.4 million by the year 2020. There are over 600,000 patients on HD in the US and an estimated 100,000 new cases are reported annually.[3] The interventions required to maintain a person on HD carry a significant financial burden, with costs estimated to be as high as $30 billion annually.[4,5] Given the increasing epidemic of obesity, diabetes, and heart disease, the burden of ESRD will continue to grow, making new interventions that can improve the social, physical, and financial realities of treating ESRD essential.

Despite the well-recognized benefits of renal transplantation, only a limited proportion of patients with end-stage renal disease can receive compatible and durable transplants; hence >60% of these patients require maintenance on hemodialysis.[4] The evaluation of hemodialysis conduits remains a critical and evolving subject. Repetitive puncture and the unique physiologic milieu of dialysis patients place a high premium on the most durable conduits for cannulation. The type of vascular cannulation used for hemodialysis has also been identified as a key determinant of survival in these patients. Professional bodies, including the Society for Vascular Surgery and the National Kidney Foundation, as well as the Centers for Medicare and Medicaid Services have recommended the use of permanent access, with an arteriovenous fistula (AVF) or arteriovenous graft (AVG) as the preferred mode of dialysis access instead of a catheter. This preference is confirmed by the lower risks of infection and hospitalization and better survival associated with the permanent access types. Temporary access is achieved with an external dialysis catheter. These catheters, which serve as a direct line from the outside of the body to the blood stream, place the patient at significant risk for bacteremia, sepsis, and death. Preventing the need or limiting the time a catheter is in place has been proven to improve patient survival.[5,6,7,8,9]

Hemodialysis is a life-sustaining therapy for patients with ESRD and it requires needle cannulation to a surgically created, high flow, vascular shunt 3-5 times per week. These shunts are created by making a direct connection between a patient's own artery and vein (AVF) or by connecting an artery to a vein with a prosthetic graft (AVG). Although AVF is the preferred mode of access, because of higher patency and lower infection rate compared with prosthetic grafts, not all patients are good candidates for an AVF because of inadequate arterial or venous anatomy.[6] In such patients, AVGs serve as alternatives. The push for increasing use of permanent access implies that surgeons and their patients are increasingly faced with the choice of competing conduits.

In the 1970s the use of expanded polytetrafluoroethylene (ePTFE) was pioneered as a suitable prosthetic graft for vascular access and it was rapidly adopted as an alternative material for connecting arteries and veins.[10,11] The ePTFE grafts require prolonged periods of healing and tissue incorporation from the point of creation to the time of safe cannulation. This period can take up to 4 weeks with standard AVGs, requiring patients to rely on the use of an external dialysis catheter for hemodialysis.

Bovine carotid artery grafts (BCA grafts) were developed for use as bioprosthetic vascular conduits in

the 1960s and became commercially available in the 1970s.[12] Several clinical studies validated their efficacy in the setting of hemodialysis, but their use lessened in popularity as alternative prosthetic conduits became available (i.e., ePTFE) and concerns for aneurysmal degeneration of BCA graft arose.[13,14] Recent improvements in the manufacturing and collagen cross-linking of these grafts have led to a recent reevaluation of their use as hemodialysis conduits. Recent advances also have been made in the design and techniques for placement and use of xenografts for hemodialysis. Progress has also been made in endovascular management of access-related complications.

Despite the widespread use of synthetic AVGs, such as ePTFE, in contemporary practice, there is little evidence to support their superiority over decellularized xenografts in this era. The need for current evidence to determine conduit choice is critical, but only two of the more recent studies directly evaluated the durability of synthetic AVG (ePTFE) vs bovine carotid artery (BCA graft) grafts for hemodialysis in recent cohorts of patients. A small, single-institution, randomized, prospective trial found no significant difference in secondary patency rates, but primary and primary-assisted patency rates were significantly higher in BCA graft than in the ePTFE grafts at 1 year.[15] This BCA graft survival advantage was most profound in the upper arm grafts with significantly higher primary and assisted patency rates. The total number of interventions and total number of angioplasties required to maintain patency were significantly fewer in the BCA graft group. The most common complication was graft thrombosis which was significantly lower in the BCA graft group than the ePTFE group. These results led the authors to conclude that the BCA graft is an excellent option for patients on hemodialysis that are not suitable for native arteriovenous fistulas, as these grafts required fewer interventions than the ePTFE grafts to maintain patency. Arhuidese et al. [16] found similar results in a larger single-institution, retrospective review of consecutive grafts. Successful graft use for dialysis was higher for BCA graft than ePTFE. However, estimates for primary and primary-assisted patency were lower for BCA graft than ePTFE at 1 and 2 years, but were not statistically significant. In contrast, secondary patency was significantly higher for BCA grafts at 1 and 2 years. Graft infection rates during the study period were not significantly different in the two graft types. The authors concluded that the results indicated better durability for the biologic graft than for ePTFE grafts in patients whose anatomy preclude placement of an AVF.

2.2 Device Background

The Artegraft® Collagen Vascular Graft™ (aka Bovine Carotid Artery (BCA) Graft™; herein referred to as Artegraft) has over 45 years of successful clinical use, with commercial clearance by the FDA in 1970 as the first peripheral vascular graft. It is currently PMA-approved (N16837) as a vascular graft for hemodialysis (Class III, product code LXA). The regulatory history goes back to the pre-amendment period; Johnson & Johnson filed an IND application in the 1960s, leading to NDA approval (#16-837) in 1970. In 1978, the FDA transferred Artegraft to the new Bureau of Medical Devices (now CDRH) as a Class III transitional device. Key regulatory milestones from 1978 to the present are listed in Table 2.

Table 3: Key Regulatory Milestones

Submission	Submission Date	Submission Purpose
PMA N16837	1985	First use of a PMA designation for approved NDA
N/A	2/1987	Ethicon, Inc, Somerville, NJ, 08876 (Division of J&J) assumes ownership of NDA 16837 and supplements, from Johnson & Johnson Cardiovascular
N/A	1/1993	Ethicon transfers all regulatory and NDA/PMA assets to Artegraft, Inc.
N16837/S020	4/2015	Approval to add labeling of "Not Made with Natural Rubber Latex" to IFU
N16837/S021	1/2016	Approval to add "non-antigenic" statement to the IFU
PMA Annual Reports (2009-2015) cover the yearly device activity period of July through August of the following year.		

Early Access

A critical factor in the survival of renal dialysis patients is the surgical creation of vascular access. Despite the fistula-first initiative, many patients will start hemodialysis using a central venous catheter (CVC). This increases the risks of associated bloodstream infections, central venous stenosis, and poorer outcomes from subsequent vascular cannulations.

Arteriovenous grafts have advantages compared with central venous catheters for dialysis and guidelines suggest their use as second choice after arteriovenous fistulas. The suggested advantages of grafts over fistulas is the ability to cannulate or access the graft earlier, traditionally 2 weeks for AVG rather than 6 weeks for AVF, and the lower rates of primary failure.

Standard practice with expanded polytetrafluoroethylene (ePTFE) grafts has been to avoid cannulation for 2 weeks following placement, but new generation grafts have been marketed for their early cannulation properties allowing use as an alternative to central venous catheters for prompt access.

Shakarchi et al.[17] performed a literature review in 2015 to define early cannulation of ePTFE vascular grafts and reported short (<72 hours) mean time to first cannulation rates for the following FDA-cleared vascular grafts:

- Acuseal: 1.3 and 2.4 days
- Flixene: 1.8 and 2.5 days

There were no reports of early cannulation for the Vectra graft; the lowest mean time to first cannulation was 14 days. Since all grafts showed similar patency and complication rates as previously published data on standard ePTFE grafts, the authors concluded that early cannulation is possible without detriment, but data did not allow specific graft recommendations. Additional support for early cannulation of ePTFE grafts was found in the clinicaltrials.gov rate reported for the Acuseal graft; 40% (54 of 135) of the grafts were cannulated within 72 hours and the rest within 7 days (NCT01173718).

The proposed BEACH Trial is a multi-center, prospective clinical trial to evaluate early access of an existing, FDA-approved bovine carotid vascular graft, approved as a general peripheral vascular graft

and for hemodialysis. The BEACH Trial is seeking to demonstrate that early access, defined as within 72 hours post implantation, of the Artegraft device results in acceptable clinical outcomes including ability to support dialysis needs thereby obviating the requirement for interim catheter placement or facilitating the removal of an existing catheter with acceptable composite major adverse clinical events (MACE) rate up to 6 months post implant.

Few vascular products approved in the 1970s have a broad level of acceptance in today's competitive market. Review of the original NDA application for Artegraft as well as the scientific literature revealed no clinical rationale for a waiting period of 14 days (for most access grafts) and 10 days (for Artegraft) before cannulation. This point was stated in the paper by Shakarchi et al.[18]: "the current literature does not seem to support the current guidelines as there is no evidence to suggest that a delay in cannulation of PTFE grafts will improve graft survival and patency." Note also that Artegraft cannot identify any scientific justification in the original NDA for the warning that was placed in the IFU to support the 10-day waiting period before cannulation.

Further, if it is assumed that dialysis is conducted 3 times per week, by allowing cannulation to the Artegraft device in the 72-hour period, only 6 to 10 additional needle punctures are added during the first 10-day period depending on whether cannulation is initiated within 72 hours, respectively. Artegraft believes that this limited number of additional early needle punctures will not significantly affect the safety or efficacy of the graft or the cannulation procedure.

Finally, graft healing should also be considered. Artegraft identified two articles that reference healing of bovine carotid vessels. Unfortunately, once this original research was conducted, all subsequent publications focus on clinical outcomes, not graft healing. These animal studies were included in Artegraft's original NDA. In 1964, Rosenberg et al.[12] presented results for dialdehyde starch cross-linked grafts from 26 dogs over a 2-year period; however, no data were reported for the initial two-week time-period.

Before this, Rosenberg[19] in 1956 presented healing data from a canine study on formalin cross-linked carotid grafts where observations were made immediately post implantation. It was noted that before 14 days the cellular reaction was not severe and was mainly at the suture line. At 21 days, the central portion of the graft was covered with a thin fibrin layer, and at 30 days a much thicker layer of new fibrous tissue supported the graft. This latter study involved formalin cross-linked tissue, not dialdehyde starch cross-linked material, as is used with the Artegraft bovine carotid graft.

The lack of short-term histological studies is common for animal investigations, since most investigators are not interested in healing immediately post implantation. Graft healing is typically studied in animal models and after longer-term implantation (i.e. >30 or 60 days). In 2007, Zilla[20] examined whether previous animal studies used the proper models to evaluate graft healing. Biological grafts are not addressed but Dacron, ePTFE and polyurethane vascular grafts were considered. The conclusions should also be similar for biological graft materials. Animal studies are typically conducted during development activities and are used to form the basis of regulatory submissions and to demonstrate the safety of a graft material.

Zilla concluded that these animal models do not represent the healing process in humans, which typically is much slower than in animal models. In addition, Zilla commented that differences in diameter and graft length as well as species differences can lead to incorrect conclusions concerning the healing process. Given this, he showed that the more rapid healing process in these animal models

still shows little or no significant healing in the two-week period post implantation. Since healing in humans is slower than in animals, it is expected that little or no healing will occur in an access graft in the initial two-week period. Graft incorporation or healing in the immediate post-implantation period should play no significant role in cannulating Artegraft in the early post-operative period and therefore is not included in the risk analysis below.

2.3 Study Rationale

Artegraft has been used as a successful dialysis graft for over 45 years. Artegraft has been used successfully with early access, defined as within 72 hours post-implant. The objective of this study is to permit Artegraft to include early access in its Instructions for use (IFU) labeling to minimize dialysis catheter use, which can lead to serious patient morbidity.

Several other vascular grafts have been cleared for early access, and rates for safety and performance are available from the scientific literature. Artegraft proposes previously published safety and performance data for the Artegraft be used for clinical context, and the expectations for each endpoint are based on these data. Safety data for perioperative (30-day post-first cannulation [Day 0]) composite MACE rates of early-access (first cannulation within 72 hours) and late-access (first access >/=10 days) Artegraft patients is the primary safety endpoint.

3.0 INVESTIGATIONAL DEVICE

The Artegraft Collagen Vascular Graft is a Class III medical device, product code LXA, and was FDA approved in 1976 (PMA N16837). The Artegraft is composed of bovine carotid artery that has been subjected to a process involving enzymatic digestion with ficin, tanning with dialdehyde starch, and sterilized with propylene oxide in its final container at elevated temperature. The manufacturing procedure has remained unchanged since its initial FDA approval except for continual refinements of the quality processes.

The intended use and design of the Artegraft remains unchanged.

As is stated in the Artegraft IFU:

"The Artegraft is intended for use distal to the aorta as a segmental arterial replacement, as an arterial bypass, as an arteriovenous shunt where more conventional methods have proven inadequate, or as an arterial patch graft.

The use of the Artegraft for femoropopliteal bypass should be reserved for those patients where the autologous saphenous vein is absent or inadequate. It is also not recommended for reconstruction across the knee joint. However, in the absence of other alternatives, the surgeon may well find the benefit to risk ratio warrants its use as an attempted limb salvage procedure."

This proposed trial is intended to support a labeling modification to state that the graft is capable of early access within 72 hours post implantation.

3.1 Preclinical Data

The preclinical data were submitted in the original NDA/PMA for the product and are applicable for the modified indication for use of the product.

3.2 Clinical Data to Date

The Artegraft device is an excellent candidate for early hemodialysis, as the biological construction of the bovine collagen matrix provides rapid exterior tissue incorporation and self-sealing qualities of the graft wall after cannulation needle removal. Over the more than 45 years of successful clinical use of the Artegraft device in hemodialysis, several publications documented the early access of the Artegraft device post implantation:

- Haimov et al.[32] described their experience in the use of 37 BCA graft for the treatment of arterial insufficiency and of 37 BCA graft for construction of arterio-venous fistulas for hemodialysis in 1974. The BCA graft was found unsuitable for use in the femoro-popliteal position, as contrasted to satisfactory follow-up in the aorto-iliac-femoral area, but it was an acceptable substitute to the autogenous saphenous vein in the construction of an arteriovenous fistula for chronic dialysis.
- Katzman et al. 1976[21] reported on 100 patients implanted with Artegraft. Grafts were routinely used within 24 hours of implantation in this population without serious consequences or excessive bleeding. A success rate of 87% was reported with thrombosis being the primary complication reported in the 13 failed implants.
  "It has also been our policy to use these grafts within 24 hours if necessary, without serious consequences and without excess bleeding, following needle withdrawal." These authors concluded that "Bovine graft arteriovenous fistulas can be used immediately."

- Johnson and colleagues[22] evaluated 100 Artegrafts in 93 patients for a period ranging from four to 102 weeks in 1976. Although complications such as thrombosis, stenosis, infection and hemorrhage occurred in 28 patients, these were similar to complications seen with other grafts. The authors commented that the Artegraft had high patient acceptance with the ability to use the graft in any patient as a means of immediate dialysis, quoting: "The main advantage of the bovine graft has been the effective use in any patient as a means for immediate dialysis. We initially preferred to wait several weeks after placement of the graft to allow for wound healing before it was used for hemodialysis. Circumstances arose, however, in which the graft had to be used within several days after surgery, and we now have dialyzed patients several hours after construction of the bovine arteriovenous fistulas. No complications have been seen from this early use of the graft, provided that meticulous hemostasis was obtained at the time of surgery and careful regulation of anticoagulants was performed during dialysis."
- Rosenberg et al.[23] also published on Artegraft for AV access use in 1976. He started dialysis on many patients immediately after Artegraft implantation. Dr. Rosenberg stated in his publication that the Artegraft "was able to be used as early as several hours to several days after placement."
- From May 1973 to April 1975, Butler et al.[30] placed 103 BCA graft in 93 patients for hemodialysis access. From April 1975 through March 1977, 184 ePTFE grafts were placed in 151 patients. There were 69 complications in the BCA grafts (67%). Although forty-nine grafts were amenable to surgical repair, twenty were replaced in these patients, eleven with PTFE grafts. With up to a two-year follow-up, we have experienced eighty-seven complications in 184 PTFE grafts [46%]. Whereas 60 grafts were successfully repaired, 27 were replaced. The overall function rate of these groups of grafts were not statistically significant. However, ePTFE grafts had significantly fewer late thromboses, increased resistance to infection, comparable longevity, and were easier to repair.
- Tellis et al. 1979[28] reported results of a retrospective study of 66 PTFE and 71 BCA grafts for dialysis access. PTFE had a higher patency rate than BCA at 12 months, was easier to work with and was easier to handle to treat infection.
- Anderson et al. 1980[27] described their results with 76 BCA graft and 100 ePTFE grafts for chronic hemodialysis arteriovenous fistulas. Cumulative patency at 1 year was 70% for the BCA graft group and 87% for the ePTFE group and at 2 years was 45 and 73%, respectively. Infection accounted for 38% of BCA graft failures and none of the PTFE failures. BCA graft required twice as many revisions per dialysis month to maintain patency as did the PTFE grafts. Graft configuration and location did not affect patency rates. Their conclusion was that the PTFE grafts appear superior to the BCA graft for construction of arteriovenous dialysis fistulas.
- Anderson et al. 2004[29] presented an abstract of retrospective comparison of graft survival and complications in chronic hemodialysis access when using bovine carotid artery versus PTFE. From 1990 to 2003, 692 hemodialysis vascular access grafts were placed in 538 patients at a single-center; 446 PTFE, 245 bovine carotid artery, and 1 cryovein grafts were used. Primary patency at one and three years for bovine was 34% and 17%, and PTFE was 36% and 13% respectively. Secondary patency for the same time intervals was 86% and 62% for bovine, and 82% and 64% for PTFE. Infection occurred in 10% of the PTFE grafts compared to only 5% in bovine (p=.01). Interventions per graft life were significantly less for bovine grafts then PTFE. Aneurysms that required treatment occurred equally in graft types, 4.1% for bovine and 6.5% for PTFE. Overall incidence of steal syndrome was 4.7%, and not significantly different between graft types.

Although secondary patency was not significantly different between the two graft types, bovine grafts required significantly less interventions than PTFE grafts to maintain their patency. Bovine grafts also had less incidence of infection and were not associated with significant aneurysmal complications. These data would suggest that bovine carotid heterograft may be a preferred material for hemodialysis vascular access grafts.

- Kennealey et al. 2011[15] compared ePTFE with BCA grafts in a prospective, randomized controlled trial at an academic medical center. They enrolled 26 patients in the BCA graft group and 27 patients in the ePTFE group. Although there was no significant difference in secondary patency rates, primary and assisted primary patency rates were significantly higher in BCA grafts than in ePTFE grafts (60.5% vs 10.1% and 60.5% vs 20.8% at 1 year, respectively). The BCA graft survival advantage was most profound in the upper arm grafts with significantly higher primary and assisted patency rates. The total number of interventions (upper arm grafts) and total number of angioplasties (overall and upper arm) required to maintain patency were significantly fewer in the BCA graft group. The most common complication was graft thrombosis which occurred at half the rate in the BCA graft group.
- From a review of 17 patients who underwent placement of BCA graft for hemodialysis access at a single institution between January 2012 and June 2013, Harlander-Locke et al. 2014[33] concluded that BCA grafts could be used as an alternative to ePTFE for angio access in patients with no available superficial vein in high-risk patients with low morbidity and good functional patency. Actuarial primary, primary-assisted, and secondary patency rates at 18 months were 73.3%, 67%, and 89%, respectively, which were superior to ePTFE as reported in the contemporary peer-reviewed literature.
- Mahajan et al.[24] presented data at a poster session at the 2016 Society for Vascular Surgery (SVS) meeting where he discussed the results for 70 patients undergoing early access of Artegraft through February 2016. At 30 days post implantation, primary and secondary patency were 77% and 94%, respectively. He concluded that "early access of bovine carotid artery graft is a viable alternative in patients with disadvantaged veins. A temporary tunneled catheter can nearly be eliminated in patients who require revision due to bleeding and aneurismal degeneration."
- Mahajan et al.[25]also published an abstract describing initial results related to early access of Artegraft with the desire to minimize the time a patient would require the use of a tunneled hemodialysis catheter. In the period from November 2013 through October 2015 Mahajan implanted 58 patients with Artegraft. Of these 58 patients, 24 (41%) underwent early access, defined as access in less than 7 days. Seventeen (29%) of these patients had successful access on postoperative day 1, one underwent access on day 4, and six underwent access on day 7. Primary and secondary patency at 30 days was 90% and 96%, respectively. There was no early graft infection, thrombosis, or bleeding. He concluded that early access of the BCA graft is an alternative in patients with disadvantaged veins and in patients who require revisions of a native fistula due to bleeding and aneurysmal degeneration, thus eliminating the need for a temporary tunneled catheter in this patient population.
- Abdoli presented the work of his colleagues (Mahajan et al. [26]) on early Artegraft access at the 31st Western Vascular Society Meeting in 2016. In this study 36 grafts were subject to early access, defined as access within seven days. Twenty-one (58%) patients were cannulated within one day. At 180 days, primary patency was 44% and secondary patency was 80%. No difference was

observed in primary and secondary patency with grafts subjected to early or standard access time. Early access resulted in an overall complication rate of 17%, whereas standard cannulation resulted in an overall complication rate of 22%.

- Malas et al. 2017[16] compared outcomes between BCA graft and ePTFE grafts for hemodialysis access in a single-institution retrospective review of 120 consecutive grafts placed in 98 patients between January 1, 2011, and June 30, 2014. Of the 120 grafts studied, 52 (43%) were BCA graft and 68 (57%) were ePTFE. Successful graft use for dialysis was 96% for BCA graft and 84% for ePTFE. Comparing BCA graft vs ePTFE, estimates for primary patency were 30% vs 43% at 1 year and 16% vs 29% at 2 years. Primary assisted patency was 36% vs 45% at 1 year and 24% vs 35% at 2 years. Secondary patency was 67% vs 48% at 1 year and 67% vs 38% at 2 years. There were no differences in primary and primary assisted for BCA graft compared with ePTFE. However, secondary patency was significantly higher for BCA graft compared with ePTFE, indicating better durability for the biologic graft than for ePTFE grafts in patients whose anatomy preclude placement of an arteriovenous fistula.
- Pineda et. al.[34] reported in 2017 the largest published experience with the current generation of BCA grafts for dialysis access and analyzed subgroups to determine the influence of obesity, gender, or prior access surgery on patency. This was a retrospective review of 134 BCA grafts implanted for hemodialysis access in the upper extremities of 126 patients between January 2012 and May 2015. For the entire group, 1-year primary patency was 32%, primary assisted patency was 49%, and secondary patency was 78%. Ten of 133 grafts (7%) developed infection requiring graft excision between 1 and 9 months after implantation. There was no statistical difference in primary or secondary patency for gender or body mass. Patients who had a BCA graft as their first access attempt had a higher primary and primary assisted patency than that of patients who had the graft placed after prior access failure. Primary patency of BCA grafts in this series was lower than that reported in a smaller randomized study, but primary assisted and secondary patency were similar.
- Abdoli et al. [2018][35] describe the performance of Artegraft implants that were cannulated early (<3 days) after implantation and associated clinical outcomes in 63 consecutive dialysis-dependent patients. 31 (49%) patients were cannulated early, and of the 31 patients cannulated early, 21 (68%) were cannulated during the first postoperative day. Early complications, primary patency, secondary patency, and tunneled dialysis catheter [TDC] incidence were monitored through clinic visits, hospital records, and survey calls to dialysis centers. The primary patency of the grafts at 1 year was 28% and 39% and secondary patency at 1 year was 74% and 77%, in the early and late cannulation cohorts, respectively. Early complications occurred in 11 (19%) patients who received an Artegraft and there were no significant differences in complication rates between early and late cannulation patients. Of the 24 patients who underwent the operation without a pre-existing TDC, only three (13%) required TDC placement during the 30-day postoperative period. These data led the authors to conclude that Artegraft implants can be cannulated early without increased complication rates or a negative impact on midterm patency and can minimize the need for a TDC postoperatively in dialysis-dependent patients undergoing primary vascular access or fistula revision procedures.

In conclusion, Artegraft has presented existing clinical data that supports early access of hemodialysis grafts and proposes a prospective study in addition to the existing clinical data and literature to support labeling for early access.

Patency

The patency data reported in all the articles reviewed for this protocol support few, if any, conclusions. Six articles were found in which Artegraft and an ePTFE graft were compared; five articles described only the performance of the Artegraft. Two articles concluded that patency rates were superior for ePTFE,[27,28] two for Artegraft[14,15] and two showed no significant difference[29,30]. Patency data reported in the literature for Artegraft are summarized (Table 3).

Since there have been changes in clinical practice over the 45 years that this graft has been marketed in the U.S., the more current articles may be weighted more highly.

Table 4: Reported Patency Data for Artegraft

Performance Parameter	Mean	Min	Max
Primary patency (%)			
3 months	81	75	86
6 months	71	69	73
1 year	46	28	73
1.5 years	66	59	73
2 years	28	16	39
3 years	25	17	32
4 years	13	13	13
Primary assisted patency (%)			
3 months	100	100	100
6 months	100	100	100
1 year	61	36	100
1.5 years	67	67	67
2 years	32	24	41
Secondary patency (%)			
3 months	100	100	100
6 months	89	89	89
1 year	76	67	89
1.5 years	89	89	89
2 years	66	64	67
3 years	62	62	62

Patency Definition from SVS Reporting Standards[31] are given below and should be used in evaluation of patency.

Primary patency. This is the interval from the time of access placement until any intervention designed to maintain or reestablish patency, access thrombosis, or the time of measurement of patency.

Assisted primary patency. This is the interval from the time of access placement until access thrombosis or the time of measurement of patency, including intervening manipulations (surgical or endovascular interventions) designed to *maintain* the functionality of a patent access (number of interventions can be represented numerically in between brackets after the actual patency of an access; i.e., assisted primary patency of 18 months [2]. This indicates that the access has been functional for 18 months but needed two interventions to maintain its functionality).

Secondary patency. This is the interval from the time of access placement until access abandonment, thrombosis, or the time of patency measurement including intervening manipulations (surgical or endovascular interventions) designed to *reestablish* functionality in thrombosed access.

3.3 Benefit/Risk Assessment

Patients who undergo implantation of the Artegraft may benefit from immediate or earlier cannulation, to limit the time required for dialysis catheter use, with the potential serious adverse effects of septicemia, sepsis, and death. The proposed change is to allow for cannulation within 72 hours post implantation. The previous label required a minimum of 10 days be allowed after implantation before puncturing the graft with needles for hemodialysis. Early cannulation may be associated with an increase in bleeding, , hemorrhage, infection, and thrombosis during initial dialysis sessions. The potential increased risks associated with early cannulation and the information to evaluate these risks are presented (Table 4).

The risks anticipated in this study are similar to those associated with currently marketed synthetic and biologic prosthetic grafts used for dialysis. The superficial site of implantation of the Artegraft, when used for dialysis, facilitates clinical and regular ultrasound monitoring of the graft, allowing any such complication to be recognized and treated promptly, thus minimizing potential risk to the patient.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of the Artegraft are in the Instructions for Use (Package Insert) in Appendix 8. The expected adverse device and procedure effects also are listed in the Safety section and in the Informed Consent. The expected events have been derived from clinical practice, literature reviews, clinicaltrials.gov results, and FDA PMA summaries for devices of this type.

Based on the risk information (Table 4), most risks are acute and identifiable during the immediate post-implantation period. We propose a multi-center, randomized, open-label treatment trial with a primary endpoint of successful Early Access, defined by three cannulations, the first one started within 72 hours post implantation, all with minimum dialysis flow rates of 250 ml/min, with a minimum 17-guage needle. Patients having cannulation within the definition of early access (i.e., within 72 hours) will be included in the primary analysis.

Artegraft will follow all study patients enrolled in the proposed clinical trial and that have successful cannulation within 72 hours as defined above, for 6 months. If follow-up is necessary at 1 year after graft implantation, it will be done via phone survey. The late-access group [>/= 10 days] will be followed to 30 days post-first cannulation. Day 0 is defined as the day of first cannulation, for early-access and late-access groups, to allow full follow-up to at least 30 days for both groups

Table 5: Risk Analysis Associated with Early Access

Risk	Timing of Potential Risk	Rating of Risk[1]	Non-Clinical Testing[2]	Relevant Clinical Endpoint
Serious Graft Infection	Typically, between 0 (surgical or device) and 180 days (cannulation)	3	none	Requires Intervention
Serious Hemorrhage / Hematoma	Between initial cannulation and 10 days	3	none	Requires Intervention
Excessive needle hole bleeding[3]	After removal of each cannula	1	none	Requires Additional Direct Pressure Time
Occlusion; primary and secondary	Ongoing with A/V access	3	none	Requires Intervention[4]
Inability to Cannulate	Immediate and up to 10 days	2	none	Continual or need for dialysis catheter

[1] Rating: 1=Minimal; 2=Mild; 3=Serious; 4=Life-threatening; 5=Death
[2] No preclinical test can be used to evaluate these clinical parameters
[3] Excess is defined as bleeding for >10 minutes using digital pressure
[4] This is routine procedure for A/V access grafts (e.g., thrombectomy)

3.3.1 Risk Mitigation

These risks will be minimized is a clinical manner applicable for all grafts and fistulas. These procedures are defined below:

- **Serious graft infection**: Standard of Care sterile procedures and antibiotic prophylaxis will be used during implantation. In addition, Standard of Care sterility procedures will be used during cannulation at the hospital or at the various outside dialysis centers.
- **Serious Hemorrhage or Hematoma**: Standard of care surgical procedures will be utilized during implantation to insure the suture lines are properly closed and Standard of Care tunneling technique will be used to insure graft incorporation. During cannulation Standard of Care procedures will be used to insure proper cannulation to avoid damage to the graft during needle insertion.
- **Excessive Needle Hole Bleeding**: This risk will be minimized by initial use of 17-gauge needles during cannulation with lower flow rates. Once the graft has healed-in, the needle size can be increased as Standard of Care dictates. After the needles are removed adequate digital pressure will be applied to stop bleeding through cannulation sites. In addition, investigators and/or research coordinators from each site will train dialysis staff to minimize this risk factor.

- **Occlusion Primary and Secondary**: As mentioned previously, occlusion of access grafts and fistulas is a common occurrence. It will be minimized using Standard of Care 17-gauge needles and the use of the largest vein on the upper arm, preferably the axillary vein to maximize blood flow through the graft.
- **Inability to Cannulate**: To minimize the risk of the inability to cannulate, the graft will be implanted near the skin, which is Standard of Care so that the graft can be easily palpated prior to needle puncture. In addition, as will be discussed later, the investigator or research coordinator at each site will meet with dialysis personnel to discuss the nature of the study and any cannulation requirements, such as the initial use of 17-gauge needles.

4.0 OBJECTIVES AND ENDPOINTS

Table 6: Study Objectives and Endpoints

Study Objective	The objective of the BEACH Trial is to demonstrate that early access of Artegraft is associated with acceptable rates of successful early access, and acceptable rates of a composite of adverse events, to support a modification of existing device labeling stating that Artegraft is capable of cannulation within 72 hours post implantation.
Primary Effectiveness Endpoint	Early access success, defined by three cannulations, the first one started within 72 hours post implantation, all with minimum dialysis flow rates of 250 ml/min pump flow rate, with a minimum 17-guage needle. Expectations: ~80% of patients in the early access group will have first cannulation within 72 hours. Expectations: ~90% of patients receiving early access will have 3 successful cannulations.
Primary Safety Endpoint	A composite of major adverse clinical events (MACE) including perigraft infection, hemorrhage, thrombosis, steal syndrome, and pseudoaneurysm within 30 days after first cannulation [Day 0] in the early-access and late-access groups. Expectation: ~20% of patients will have at least one MACE event; no significant difference in event number or type between early and late access groups. All MACE will be adjudicated by an independent accessor.
Secondary Effectiveness Endpoints	Patency (Primary, Assisted Primary, and Secondary) at 30 days after first successful cannulation [Day 0], and at 12 weeks and 6 months after implantation in the early-access group and at 30 days post-Day 0 in the late-access group. The late access group will also be assessed for patency at 6 months through a telephone interview or office visit to provide a more robust data set. Expectations: • Patency rates [all 3 types] at 30 days will be similar in the early and late access groups. • We expect primary patency to be ≥85%, ≥75% and ≥65% at 30 days, 3 months, and 6 months, respectively. • Primary-assisted patency rates at 30 days, 3 months, and 6 months will be ≥85%. • Secondary patency rates will be ≥90% and ≥90% at 3 and 6 months, respectively.

Secondary Safety (for information only)	All adverse events will be collected in the early-access group [to 6 months] and the late-access group [to 30 days post Day 0] and summarized by unique event, seriousness, and relationship to device or procedure. All serious adverse events will be adjudicated by an independent accessor.
Secondary Catheter Removal Endpoint (for information only)	The number of days from graft implant or fistula revision to catheter removal shall be recorded.

5.0 CLINICAL INVESTIGATION DESIGN

5.1 Overall Design

This is a multi-center, open-label fixed treatment study where eligible patients will have early access, defined as within 72 hours post implantation, of the Artegraft device. A limited number of patients who opt out of the early access procedure due to patient-related factors will be followed only to 30 days post-Day 0 in this study to assess perioperative MACE and patency rates [>/= 10 days; late-access group]. Patients who sign the informed consent and fulfil the eligibility criteria will be enrolled in the clinical study. Patients with early access will be followed for 4, 12- and 26-weeks post implantation. Patients with late access will be followed to 30 days post Day 0. The late access group will also be assessed for patency at 6 months through a telephone interview or office visit to provide a more robust data set. To ensure that all required data are captured, the sites will be trained on data capture and monitored through clinic visits, hospital records, and survey calls to dialysis centers. Refer to the monitoring plan for more detail.

5.2 Scientific Rationale for Study Design

The rationale for the proposed clinical study is based on the following:

- Artegraft has been used as a successful dialysis graft for over 45 years.
- Artegraft has been used successfully with early access, defined as within 72 hours post implantation. The objective of this study in to permit Artegraft to include early access in its Instructions for use (IFU) labeling to minimize dialysis catheter use, which can lead to serious patient morbidity.
- No significant healing occurs in the initial 14-day post-implantation period.
- With early access within 72 hours), there will be a maximum of only 10 additional cannulations.
- No scientific data can be found to justify the current 10 days or recommended 14-day waiting period for vascular access grafts.
- Overall, there is minimal risk for this requested change to the IFU; most identified risks are acute, and the risks will be evaluated during this proposed clinical trial.

5.3 Clinical Investigation Population

The population for this clinical investigation will include patients who have end stage renal disease (ESRD) and require vascular access for hemodialysis.

5.4 Study Completion Definition

An early-access patient is considered to have completed the study if all phases of the study, including the 6 month visit have been completed. Study completion is when 50 patients who started with successful early access (defined by three cannulations, the first one started within 72 hours after implantation, all with minimum dialysis pump flow rates of 250 ml/min have been assessed to 6 months. In the late-access group (first access at >/= 10 days), 25 patients will be followed for 30 days post-first access [Day 0] for MACE and patency information. The late access group will also be assessed for patency at 6 months through a telephone interview or office visit to provide a more robust data set.

6.0 PATIENT SELECTION AND WITHDRAWAL

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

A protocol deviation is any noncompliance with the protocol or GCP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. If there are protocol deviations, corrective actions are to be developed by the site and implemented promptly. Although it is in principle not allowed to deviate from the protocol, under emergency circumstances, deviations may proceed without prior approval of the sponsor and the IRB to protect the rights, safety, and well-being of human subjects.

All protocol deviations, with no regard if they are assessed as major or minor, will be documented and reported by the CRO during the study in the Monitoring Reports. Major deviations will be reported to the sponsor who will agree on the necessary actions to be taken. If required per their guidelines, reports about protocol deviations must be reported to the local IRB.

Any patients in the late access group who require cannulation prior to the 10-day cannulation period will receive Standard of Care treatment. Dialysis will be initiated using an existing dialysis catheter or after placement of a new dialysis catheter. Hemodialysis with Artegraft will commence after the 10-day waiting period.

Any patients that are in the early access group that are not cannulated within 72 hours shall be replaced by additional patients using the randomization plan until the 50-patient number is reached.

6.1 Inclusion Criteria

Patients are eligible to be included in the study only if they meet the following criteria:

1. Male or Female, 18 years or older
2. Diagnosis of End Stage Renal Disease (ESRD) and require vascular access for hemodialysis
3. Native [autogenous tissue] AV fistula creation or access is not indicated or non-viable [disadvantaged veins]
4. Requiring repair of an existing fistula or conduit, but only if using Artegraft as an interposition placement and the Artegraft is cannulated [not the fistula]. Artegraft must be place in a fresh subcutaneous tunnel. Thigh loop grafts will not be used.
5. Able to accommodate vascular graft placement in the upper extremity (i.e., forearm, or upper arm)
6. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF)
7. Able and willing to comply with the study protocol
8. Agrees to initiate and maintain hemodialysis treatments
9. Life expectancy is > 1 year based on physician assessment

6.2 Exclusion Criteria

Patients are excluded from the trial if any of the following criteria apply:

1. High grade central venous stenosis/occlusion
2. Breast-feeding, pregnant or planning pregnancy within next 12 months.
3. Non-resolved infected existing grafts
4. Documented sepsis/bacteremia by blood culture within 4 weeks of implantation.
5. History of non-controlled immunodeficiency syndrome, including AIDS/HIV; Active clinically significant immune-mediated disease, not controlled by low-dose maintenance immunosuppression. The diagnosis of HIV alone, provided adequately treated, is not a contraindication for enrolment.
6. Severe liver dysfunction and/or coagulation or bleeding disorders.
7. Elevated platelet count > 1 million cells/mm3
8. History of heparin-induced thrombocytopenia syndrome (HIT)
9. Documented hypercoagulable state
10. Currently participating in another investigational drug or device study which may clinically interfere with any endpoints of this trial
11. Known hypersensitivity or contraindication to device materials or procedural medications that cannot be adequately managed medically
12. History or evidence of severe cardiac disease (NYHA Functional Class III or IV), , myocardial infarction within 6 months of enrollment, ventricular tachyarrhythmias requiring continuing treatment, or unstable angina, uncontrolled CHF
13. History or evidence of severe peripheral arterial disease in the extremity selected for implant (i.e. arterial inflow insufficient to support hemodialysis)
14. History of cancer with active disease or treatment within the previous year, except for non-invasive basal or squamous cell carcinoma of the skin
15. Bleeding diathesis, other than that associated with ESRD
16. Scheduled renal transplant within 6 months
17. Patients who require chronic anticoagulation except for antiplatelet therapy. Patients currently receiving or who have received within the last month direct thrombin inhibitors, factor Xa inhibitors, or vitamin K antagonists should not be included in the study.

6.3 Patient Recruitment and Screening

Investigators and site locations have been chosen based on experience with the implantation of Artegraft, patient population available to minimize enrollment time, and geographic distribution of sites around the US. The chosen sites also have a positive record of enrollment for clinical trials involving AVGs.

Investigators will approach potential patients with the best interest of the patient in mind and will adhere to the US Federal Regulation {CFR) and Good Clinical Practice (GCP). Each investigator must

adhere to all requirements stipulated by their respective IRB. This includes notification to the IRB regarding protocol amendments, updates to the subject informed consent, recruitment materials intended for viewing by patients, investigational device safety reports, SAEs and unexpected AEs, reports and updates regarding the ongoing review of the trial at intervals specified by the respective IRB, and submission of final study reports and summaries to the IRB.

6.4 Early Withdrawal of Patients

A patient may withdraw from the study at any time at their own or their physician's discretion. If withdrawal occurs before the Week 26 visit, the patient will be asked to complete an early termination visit at which all assessments normally performed at Week 26 will be completed. The reasons for early termination should be recorded in the CRF.

6.5 Patient Restrictions

There are no patient restrictions on diet, caffeine, alcohol, tobacco, or activities, other than those for medications they are currently taking.

6.6 Patient Withdrawal

Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure, and any serious adverse event (SAE).

Individuals who do not meet the entry criteria for participation in this study (screen failure) may not be rescreened.

6.7 Duration of Clinical Investigation (expected duration of patient participation)

The early-access patient enrollment duration is expected to be 3-6 months, so total study duration is expected to be 12 months. During the enrollment period, 25 patients also will be enrolled in the late-access group which will be for a duration of 30 days post first cannulation [Day 0]. The late access group will also be assessed for patency at 6 months through a telephone interview or office visit to provide a more robust data set.

6.7.1 Regulatory Trial Duration

The primary performance and safety endpoints will be evaluated from the start of dialysis (Day 0) for all patients, at 4, 12 and 6 months for the early-access group, and at 30 days post Day 0 for the late access group. Since these patients have dialysis sessions several times per week, it is anticipated that endpoint data will be collected throughout the trial period for each group.

6.7.2 Overall Trial Duration

The enrollment goal is ≥3 patients per site, per month. The early-access patient enrollment duration is expected to be 3-6 months, so total study duration is expected to be 12 months..

The follow-up period on the early access patients will be 6 months and 30 days on the late access patients. In addition, a follow-up telephone call, based on a questionnaire, will be made to the early access patients and/or dialysis centers to determine if any unexpected complications had occurred during the 6-12 month period. For this reason, all patients will be consented to 12 months. The late access group will also be assessed for patency at 6 months through a telephone interview or office visit to provide a more robust data set.

Beyond the 12 month anticipated trial period, data will be collected by Artegraft until the last patient has completed the trial. Beyond the trial, Artegraft's Standard Operating Procedures for adverse event reporting and monitoring will be continued for all patients

6.8 Number of Patients Included in Clinical Investigation

A total of 50 patients will be enrolled, successfully provided early cannulation within 72 hours and followed to 6 months. This sample size is logistically rather than statistically driven. Patients randomized to the early access group not cannulated in the <72-hour period will still be followed for 30 days after first cannulation. It is estimated that up to 10 additional patients may fall into this category.

It is expected that 25 enrolled patients will have late access [>/= 10 days] of the Artegraft. These patients will be followed only to 30 days post Day 0 to assess perioperative MACE and patency rates. The late access group will also be assessed for patency at 6 months through a telephone interview or office visit to provide a more robust data set.

6.9 Enrollment Period (time needed to select # of patients)

Artegraft anticipates that with use of high-volume study sites, it will be possible to complete enrollment within 3-6 months.

7.0 STUDY DEVICE

7.1 Intended Use

The intended use and design of the Artegraft is unchanged.

The Artegraft is intended for use distal to the aorta as a segmental arterial replacement, as an arterial bypass, as an arteriovenous shunt where more conventional methods have proven inadequate, or as an arterial patch graft.

The use of the Artegraft for femoropopliteal bypass should be reserved for those patients where the autologous saphenous vein is absent or inadequate. It is not recommended for reconstruction across the knee joint. However, in the absence of other alternatives, the surgeon may well find the benefit to risk ratio warrants its use as an attempted limb salvage procedure.

7.2 Device Manufacturer

Artegraft, Inc, 206 North Center Street, North Brunswick, NJ 08902 manufactures the Artegraft BCA graft.

7.3 Device Description

The Artegraft can be used as a primary vascular conduit or may be used for revision of an existing vascular conduit. One of the primary uses of the Artegraft Bovine Collagen Vascular Graft is for the creation of a subcutaneous arteriovenous conduit (typically in the upper or lower arm) for hemodialysis.

The Artegraft is composed of a 4 – 7 mm inner diameter (ID) bovine carotid artery which has undergone specific manufacturing processes to make it suitable for human implantation. The controlled processing provides an essentially pure collagen matrix conduit, of biologic construction with a fibrocollagenous outer and inner surface (adventitia) with qualities for early tissue incorporation into the exterior graft matrix. The collagen matrix provides a natural, resealable graft wall after fistula needle removal.

The finished graft is non-antigenic, non-pyrogenic, and provided sterile to the user in an alcohol-based storage solution.

7.3.1 Device Sizes

Table 7: Device Code and Sizes

Product Code	Description	
	Inner Diameter	**Minimum Length**
	Outer Diameters vary, but typically 1 mm larger	
AG 535	4 mm	35 cm
AG 540	4 mm	40 cm
AG 616	5 mm	15 cm
AG 630	5 mm	30 cm
AG 636	5 mm	35 cm
AG 640	5 mm	40 cm
AG 645	5 mm	45 cm
AG 715	6 mm	15 cm
AG 730	6 mm	30 cm
AG 735	6 mm	35 cm
AG 740	6 mm	40 cm
AG 745	6 mm	45 cm
AG 750	6 mm	50 cm
AG 840	7 mm	40 cm
AG 845	7 mm	45 cm
AG 1015	8 mm	15 cm
AG 1030	8 mm	30 cm

7.4 Treatment Regimen

The Artegraft has been in commercial distribution and clinical use for more than 45 years. It will be implanted per standard institution procedures by trained vascular surgeons, according to the Instructions for Use (Appendix 8). Dialysis regimens are also per the standard institutional practice and are done by trained personnel.

Medical device malfunctions, including those resulting from device malfunctions will be detected, documented, and reported by the Investigator throughout the study, per the safety section below. Device malfunctions expected for product code LXA (from the FDA TPLC database) are: leak (hole, break, material integrity), obstruction (occlusion), and compromised packaging.

7.5 Device Traceability

Device lot numbers will be tracked on the CRF.

7.6 Method of Assigning Patients

Patients will be randomized in a 2:1 ratio to either early or late vascular access. The randomization will be stratified by investigative site, and will use a random permuted block design within strata, with blocks of size 3 and 6 ordered randomly within site.

Once a patient signs informed consent, is determined to meet the inclusion/exclusion criteria, and is successfully implanted with the Artegraft, the site designated staff will open an envelope to determine the randomization number and whether the patient is randomly allocated to early or late vascular access.

7.7 Training to Use Medical Device

The Investigator and/or Research Coordinator will meet with dialysis center staff to discuss the Artegraft device, the nature of the study, and any special requirements related to the cannulation of the Artegraft, in particular for early access patients.

It is imperative that all adverse events in each patient implanted with the Artegraft are captured for this study. The dialysis center staff will notify the Investigator or Research Coordinator should an adverse event occur. The Research Coordinator will be trained by IQVIA Biotech staff to record adverse events and device malfunctions via the Adverse Event Case Report Form. The report will include, whenever possible, severity, duration, outcome, and the Investigator's medical judgment as to the relationship of the adverse event to the study device, procedure, or underlying disease (i.e., not related, possibly related, or definitely related). IQVIA Biotech (formally Novella Clinical) will train investigator site personnel in proper completion of all electronic data forms prior to initiation of the study.

All SAEs and device malfunctions that could have led to a SADE must be reported to the Sponsor or its Contract Research Organization (CRO) within 1 business day of the Investigator's knowledge of the event using the SAE report or other appropriate form. IRB notification of the AE may also be required, depending on the conditions of approval or requirements of the respective committee.

Refer to the data handling section for more information.

Since there are no differences in the cannulation technique or care for early access of Artegraft as compared to current cannulation techniques, Artegraft will utilize existing Artegraft, Inc. biological graft cannulation training materials including a Cannulation Wall Chart[36] and training video[37] to help train dialysis staff on cannulation technique. This material is currently available on the Artegraft web site.

The dialysis staff at each participating dialysis center will be informed of the study so they will be aware that patients from the study will be treated at their facility. The Investigator and/or Research Coordinators will meet with the dialysis center staff and instruct the dialysis staff on cannulation technique based on reference material described above, if required. Initial cannulation is performed with 17-gauge needles with lower dialysis flow rates which is Standard of Care for biological grafts and fistulas. Needle size and flow rates can be increased as the graft incorporation progresses.

7.8 Implantation of Study Device (Procedures)

Patients will be implanted with the Artegraft in the upper arm (arterial anastomosis to the brachial artery, venous anastomosis to the axillary, brachial or basilic vein) using standard vascular surgical techniques. Placing the graft across the elbow will be avoided.

Alternate implantation sites in upper extremity normally used in dialysis access are also acceptable if clinical assessment justifies an alternate site.

The Artegraft Vascular Graft is implanted using standard vascular surgical techniques similar to placement of predicate peripheral vascular prostheses. Implantation of the graft will be undertaken by qualified surgeons experienced in dialysis access surgery. The Artegraft is implanted following the Instructions for Use.

7.9 Patient Compliance Monitoring

This is a permanent implant that will be used for dialysis and assessed clinically multiple times per week. Patient compliance is not relevant.

7.10 Packaging

Artegraft is packaged in a specially-designed tube containing a sterilizing solution. The container system meets container/closure requirements to maintain sterility and product integrity. The graft container is shipped in an outer box with a specially designed insert to protect it during shipping. Refer to the Artegraft IFU for packaging and preparation instructions. Package shall reflect that the Artegrafts used in the study shall be identified as Investigational Devices.

7.11 Receiving, Storage, Dispensing of Study Device

Since the trial devices are already cleared to market, this section is not applicable.

7.12 Study Device Compliance

This section is not applicable.

7.13 Prior and Concomitant Therapy

Prior medications or vaccines (including over-the-counter or prescription medicines, vitamins, or herbal supplements) are defined as all medications taken within 7 days (whether continuing or not) before Day 0. All prior and concomitant medications (including immediately pre-surgery and post-surgery medications) must be listed in the patient's medical record and recorded on the CRF. Patients should be questioned at each study visit concerning any new medications or changes in current medications.

Note: particular attention should be made to identify the use of antithrombotic or antiplatelet agents (e.g., prasugrel, direct thrombin inhibitors, factor Xa inhibitors, or vitamin K antagonists).

For each medication taken, the following information will be collected:

- Medication generic name / components of combination product
- Route of administration
- Date started
- Date stopped

- Indication for use

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.14 Essential, Precautionary, and Prohibited Medications

These should follow the guidelines of the treating institution. The following are general considerations.

Essential Medications: All patients should receive both antibiotic and antithrombotic prophylaxis in conjunction with graft implantation.

- Antibiotic: All patients should receive antibiotic prophylaxis within 30-60 minutes before skin incision. The preferred choice is cephazolin 1-2 g and vancomycin 1 g given intravenously (IV) just before surgery If the patient is allergic to beta-lactam drugs an alternative regimen complying with local antibiotic prophylaxis guidelines should be used.
- Antithrombotic:
  - Intra-operative is up to the discretion of the implanting investigator
  - Aspirin 71 to 325 mg daily (orally) starting on the day after surgery and continuing long term while the graft is in place
  - If the patient is unable to take aspirin or if clopidogrel is required for other clinical reasons, then clopidogrel 75 mg daily may be used instead.
  - Other thromboprophylaxis is at the discretion of the investigator

Prohibited Medications: : Patients who require chronic anticoagulation except for antiplatelet therapy. Patients currently receiving or who have received within the last month direct thrombin inhibitors, factor Xa inhibitors, or vitamin K antagonists should not be included in the study. These drugs should be avoided in the immediate post-surgical period until wound healing has occurred and the use of the graft for dialysis commences.

Restricted Medications: The combination of aspirin plus clopidogrel should be used only where there is a specific clinical indication for its administration. Direct thrombin inhibitors, and vitamin K antagonists should only be given postoperatively if there is a specific indication for their use. They should be avoided, if possible, until the surgical wound has healed and the use of the graft for dialysis commences.

7.15 Rescue Therapy

Standard of care should be used to maintain functionality of the Artegraft.

7.16 Treatment after the End of the Study

After the final examinations, the patients do not get any further study-specific treatment. They will be treated by their medical doctor in a way that is appropriate for them. The Artegraft can be used for dialysis as long as it is functional.

8.0 STUDY PROCEDURES

Study procedures and schedule of assessments, are summarized below and in Table 1.

8.1 Screening – Day -45 to Day of Surgery

The following procedures will be done during the screening period:

- Eligibility (inclusion/exclusion)
- Informed Consent
- Medical History
- Prior and concomitant medication
- Physical Exam
- 12-Lead ECG
- Vessel mapping
- Pregnancy test (Serum; women of child-bearing potential only; to be assessed within 7 days of implant)
- Hematology and coagulation lab test
- Clinical chemistry lab test

8.2 Implantation (Day of Surgery)

- Eligibility (inclusion/exclusion) (if not already obtained)
- Informed Consent (if not already obtained or if change in eligibility occurs)
- Medical History (if not already obtained or if change in medical condition occurs)
- Prior and concomitant medication (if not already obtained)
- 12-Lead ECG (if not already obtained)
- Surgical implant of Artegraft
- Documentation of surgical procedure
- Adverse event assessment
- Medical device malfunctions
- Documentation of graft interventions (angioplasty, stenting, thrombectomy, thrombolysis, revision)

Before discharge the patient will be instructed to contact the study staff promptly if he/she develops new or increasing pain, redness, local swelling or bruising around the surgical site or the graft or any generalized swelling of the operative arm. If such symptoms occur and the investigator considers that they might be clinically significant an immediate follow up visit should be scheduled.

Each patient will be provided with contact information for use in such circumstances. These instructions will be repeated at every study visit. The dialysis unit treating the patient will be notified that the patient is participating in the study and will be asked to contact the study staff urgently if they have any concerns about the graft.

<u>Dialysis Procedures</u>

These patients will be having dialysis every few days – assessments should be the same or similar at <u>each</u> post-implant visit. Dialysis should be initiated (Day 0) using small needles (max of 17G). This needle size should be used for at least the first week of dialysis using the Artegraft. After 1 week, the needle size may be increased and standard needles (no greater than 14G) may be used. Needle

placement sites should be rotated using a ladder technique to allow healing of the graft to occur and thus minimize the possibility of pseudoaneurysm formation or complication.

8.3 1 – 17 Days Post Day 0

- Dialysis access first use [Day 0]
- Prior and concomitant medication
- Physical Exam
- Assessment of wound healing
- Graft patency assessment
- Adverse event assessment
- Concomitant medication
- Medical device malfunctions
- Documentation of graft interventions
- Dialysis catheter status and use

8.4 30 ± 3 Days Post Day 0

- Physical Exam
- Assessment of wound healing
- Graft patency assessment
- Adverse event assessment
- Concomitant medication
- Medical device malfunctions
- Documentation of graft interventions
- Dialysis catheter status and use

8.5 12 weeks ± 7 Days Post Day 0 (early-access subjects only)

- Physical Exam
- Assessment of wound healing
- Graft patency assessment
- Adverse event assessment
- Concomitant medication
- Medical device malfunctions
- Documentation of graft interventions
- Dialysis catheter status and use

8.6 6 months ± 7 Days Post Day 0 (early access subjects only; late-access subjects will be assessed for patency only)

- Physical Exam
- Assessment of wound healing
- Graft patency assessment
- Adverse event assessment
- Concomitant medication
- Medical device malfunctions

- Documentation of graft interventions
- Dialysis catheter status and use

8.7 12 months ± 14 Days Post Day 0 (early access subjects only)

- Graft patency assessment
- Adverse event assessment between 6 months and 12 months

9.0 STATISTICAL PLAN

9.1 Sample Size Determination

The sample size for this study is logistically rather than statistically driven.

A total of 50 patients will be enrolled, randomized and successfully provided early cannulation within 72 hours, and followed to 6 months. Another group of 25 patients will be randomly assigned and provided cannulation for 10 or more days after implant and followed only to 30 days to assess perioperative MACE rates. No loss to follow-up is projected at 30-days post implantation.

Previously published patency data (refer to the background section above) will be used at 12 weeks and 6 months for clinical context. The early access study group results will be compared with these previously published data, which were reported for Artegraft normal cannulation times. It should be noted that complications may or may not result in an early access failure. Confidence intervals will be presented around each endpoint. The observed rates will be numerically compared with the expected rates and no formal statistical hypothesis will be tested.

9.2 Statistical Methods

9.2.1 Overview of Statistical Analysis

Descriptive statistics will be performed separately for the early and late access treatment groups. The estimated patency rates will be calculated using the SVS reporting standards guidelines.[31] Should there be considerable site differences and with sufficient number of patients within sites, stratified and/or weighted estimates may be performed.

9.2.2 Estimating primary effectiveness and primary safety endpoints

The percentage of patients with primary effectiveness success rates as defined in section 4 will be reported by randomized groups. The 95% confidence interval (CI) calculated using the Clopper-Pearson[2] exact method for binomial data will be reported by randomized groups. No formal statistical testing of the differences in primary effectiveness rates by randomized groups will be performed.

Similarly, the percentage of patients with MACE together with its 95% CI calculated using the Clopper-Pearson exact method will be reported by randomized groups. The number and percentage of patients in each of the MACE components will also be reported by randomized groups.

9.2.3 Estimating patency rates and time to catheter removal

If possible, the estimated patency rates will be calculated using the SVS reporting standards guidelines.[31] Kaplan-Meier (KM) survival curves will be used to estimate patency.

In figures, the numbers of patients at risk at the start of each interval (periodically for the KM) must be included and the standard error for each estimate of patency must be displayed with bars. When the standard error of the patency rate estimate exceeds 10%, the curve either should not be drawn or should be represented with a dotted line as a means of indicating lack of reliability of the estimate. If warranted, Cox hazard regression analysis may be performed where major risk factors identified during screening/baseline compromise the explanatory variables.

Time to catheter removal will be analyzed using the KM and/or Cox hazard regression as described above.

9.2.4 Patient Populations for Analysis

Five analysis populations will be defined for use with various analyses. The following table illustrates the relationship between each population and the analyses for which the data from the population will be used.

Table 8: Patient Population for Analysis

Analysis Population	Analysis				
	Baseline	Patient Disposition	Effectiveness/ Performance	Safety	Product Use
Screened		X			
Intent-to-treat (ITT)	X	X			
Safety				X	X
Effectiveness			X		
Per-protocol			X[†]		

[†] Analysis done only if any data from more than 5% of effectiveness analysis population patients are excluded from this population.

9.2.5 Screened

The screened analysis population will include patients who signed the informed consent and were assessed for meeting the inclusion/exclusion criteria. The screened analysis set will be used in reporting the study disposition of study participants.

9.2.6 Intent-to-treat (ITT) Analysis Population

The Intent-To-Treat (ITT) analysis population in this prospective randomized study may include a small subset of patients in the screened analysis population who meet the inclusion/exclusion criteria and are randomized to either early or late vascular access but received cannulation outside their specified time period. The ITT analysis population will be used in reporting outcomes based on their randomized access time and not on the access time they received. In other words, all participants who are randomized are analyzed according to the group they were originally assigned, regardless of what access time (if any) they received.

9.2.7 Safety

The safety analysis population will include a subset of patients in the screened analysis population who are implanted with the Artegraft, regardless of whether randomized early or late vascular access is performed. The safety analysis population will be used in reporting safety and product use characteristics.

9.2.8 Effectiveness

The effectiveness analysis population will include a subset of the ITT analysis population who are implanted with the Artegraft based on the randomized early or late vascular access with the applicable

performance/effectiveness responses reported for each randomized group. The effectiveness analysis population will be used in reporting the performance /effectiveness of the randomized early or late vascular access groups.

9.2.9 Per-protocol

The per-protocol analysis population will include a subset of patients in the effectiveness analysis population with no pre-specified major protocol violations or deviations. The per-protocol analysis population will be used in reporting the performance /effectiveness of the randomized groups, if the number of patients in this analysis population differs from the number of patients in the effectiveness analysis population by more than 5 percent.

9.3 Patient Discontinuation/Withdrawal from the Study

- A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.
- See SoA (Table **1**) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

9.4 Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The study center must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

10.0 SAFETY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table **1**).
- Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA (Table **1**), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the period defined in the SoA (Table **1**).

10.1 Safety Assessments

10.2 Adverse Events

The definitions of SAE can be found in Appendix 4.

Adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) or may be obtained from the patient's dialysis center.

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study device or study procedures, or that caused the subject to discontinue the Artegraft device(see Section 8.0 Study Procedures).

Expected Adverse Events

Table 9: Expected Procedure-Related Adverse Events

Bleeding
Death
Disruption or tearing of the suture line, graft, or host vessel
Embolism
Graft redundancy
Intervention complication (e.g., venous rupture)
Occlusion
Pain
Thrombosis
Technical complications (anastomosed to diseased vessel; graft physically compressed; incorrect sizing; implant technique; radiology infiltrated graft; bleeding from native vessel)

Table 10: Expected Device-Related Adverse Events

Access failure; loss of access
Aneurysm
Bleeding
Cannulation-associated complication / trauma
Death
Embolic event
Graft dilatation
Hand ischemia, acute
Hand ischemia, subacute (delayed but w/in 1 month of implant)
Hematoma
Hemorrhage
Infection (cellulitis, abscess, septic emboli, bacteremia, sepsis)
Intervention (surgical, angioplasty, stenting, thrombectomy, thrombolysis, revision)
Inflammation / sensitivity to device materials
Invasive surgical procedure
Kinking
Low flow
Neointimal hyperplasia
Pain
Primary graft failure
Pseudoaneurysm
Seroma
Skin erosion; lesion
Slow wound healing
Steal syndrome
Stenosis
Swelling of the implanted limb
Thrombosis / occlusion, graft
Thrombosis, other
Ultrafiltration

All AEs will be collected from the start of treatment until the final follow-up visit at the time points specified in the SoA's (Table 1a and Table 1b).

Medical occurrences that begin before the graft implantation procedure, but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study device or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

10.2.1 Method of Detecting AEs and SAEs (Recording of Adverse Device Effects)

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences. The graft sites will be assessed for all adverse events during each dialysis treatment.

10.2.2 Investigator Reporting: Notifying the IRB

It is the responsibility of each investigator to submit the protocol, IFU, subject informed consent, subject recruitment materials (if applicable), and other documentation as required by the IRB to their IRB for review and approval. A copy of the written approval must be provided to the contract research organization (CRO). The documentation should clearly mention the approval/favorable opinion of the protocol, the subject informed consent form, and subject recruitment materials (if applicable), including respective version dates. The written approval and a list of members, their titles or occupations, and their institutional affiliations must be obtained from the IRBs and provided to the CRO prior to the release of clinical study supplies to the investigational site and commencement of the study. If any member of the IRB has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained.

Each investigator must adhere to all requirements stipulated by their respective IRB. This includes notification to the IRB regarding protocol amendments, updates to the subject informed consent, recruitment materials intended for viewing by subjects, , SAEs and unexpected AEs, reports and updates regarding the ongoing review of the trial at intervals specified by the respective IRB, and submission of final study reports and summaries to the IRB.

10.2.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs, (and non-serious AEs of special interest (as defined in Section 10.2.5)), will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 9.4). Further information on follow-up procedures is given in Appendix 4.

10.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study device under clinical investigation are met.

- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study device under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it in the study documentation and will notify the IRB, if appropriate according to local requirements.

10.2.5 Adverse Events of Special Interest

The adverse events of special interest are those of the composite safety endpoint, which include major adverse clinical events (MACE) (e.g., perigraft infection, hemorrhage, , steal, thrombosis, and pseudoaneurysm) within 30 days after first cannulation [Day 0] in the early-access group and in the late-access group.

10.2.6 Stopping Rules

The FDA cleared this device and it has been on the market for more than 40 years. Justifications of the following stopping rules are based on previously published safety data for Artegraft.

Stopping Rules include:

- MACE in more than 20% of early-access patients within 30 days of Day 0
- MACE not listed in Table 4 in early-access patients
- Any SAE not listed in Tables 8 and 9 in early-access patients

10.2.7 Medical Device Malfunctions

Medical devices are being provided for use in this study to define safety and performance of the Artegraft for early access. To fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of incident or device malfunction that occur during the study with such devices. Device malfunctions expected for product code LXA (from the FDA TPLC database) are: leak (hole, break, material integrity such as to cause true or pseudo aneurysm) and compromised packaging.

The definition of a Medical Device Incident can be found in Appendix 5.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 10.2.2 and Appendix 4 of the protocol.

10.2.7.1 Period for Detecting Medical Device Malfunctions

- Medical device malfunctions or device malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the Investigator learns of any incident at any time after a patient has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.

The method of documenting Medical device malfunctions is provided in Appendix 5.

10.2.7.2 Follow-up of Medical Device Malfunctions

- All medical device malfunctions involving an AE will be followed and reported in the same manner as other AEs (see Section 10.2.2). This applies to all patients.
- The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

10.2.7.3 Prompt Reporting of Medical Device Malfunctions to Sponsor

- Medical device malfunctions will be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of a medical device incident.
- The Issue Management Form will be sent to the Sponsor by email to communication@artegraft.com. If email is unavailable, then the phone number 800-631-5264 (for registering the incident) should be used.

10.2.7.4 Regulatory Reporting Requirements for Medical Device Malfunctions

- The Investigator will promptly report all incidents occurring with any medical device provided for use in the study for the Sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The Investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB.

10.2.8 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set.

10.2.9 Missing Data

Data from patients who withdraw from the study, including AEs and any follow-up, will be included in the analyses of primary and secondary outcomes.

10.3 Interim Analyses

No interim analyses for safety or efficacy are planned.

10.4 Safety Monitoring

The principal investigator at each site will perform the initial characterization of each serious event. Reports of serious events will be sent to an independent assessor with expertise in vascular access devices who will evaluate serious device related events, MACE, or device malfunctions for level of seriousness and relationship to device or procedure. Reports of serious adverse events also will be reported to each IRB.

An independent accessor will be established to enhance the safety of subjects participating in the study. The accessor will adjudicate all possibly and definitely device and procedure-related serious adverse events and will act as an advisor to Artegraft through the CRO. Individual will be represented from the one of the key medical disciplines involved with the care of ESRD patients and management of AV access. Accessor will not be directly involved with the clinical trial and all will possess experience with clinical trial participation or management in the ESRD or AV access space. Accessor's primary responsibilities are to monitor the safety of trial participants, to review safety-related data, to evaluate the frequency and severity and device-relatedness of adverse events, and to consider external data throughout the duration of the trial, and to make recommendations on trial changes.

11.0 DATA HANDLING AND RECORD KEEPING

Data will be collected through an electronic data capturing system on the e-CRF, a secure, internet-based CRF and image transfer software. This system will be used to record all patient information collected in the study for secure data tracking and centralised data monitoring ("remote monitoring").

Automated, real time data analyses built into the database enable complete control on study outcomes and safety assessments. Automated alerts (emails) are generated by the system for enrollment of patients, AE notification, and upcoming or late follow up visits. Additional specific alerts and reports may be setup as required by the Sponsor to ensure full control and easier compliance to the protocol.

The principal investigator or designated site staff (e.g. co-investigators, research/study coordinators or study nurses) at the clinical site will perform primary data collection by entering the data into the e-CRF, using a standard internet-browser. Only the principal investigator or other pre-designated clinical investigation site personnel will be authorised to enter data (from source documents) via internet-based e-CRF, using a unique user name and pass code. Clinical investigation site personnel will each be assigned a unique user name and pass code to access the e-CRF. Each user access to the system is tracked, so that all data operations can be monitored and verified.

The Sponsor's designated monitor shall ensure appropriate training is provided before the start of the clinical investigation to all site personnel involved.

The principal investigator can delegate tasks to his/her collaborators; however, the roles and responsibilities and period of involvement for each clinical site personnel must be documented on the site personnel log as well as training received before getting involved with the clinical investigation.

Clinical site personnel not trained and not officially identified by his/her name, signature and personal login for the EDC system cannot access the system nor enter data in the e-CRFs.

The principal investigator or delegated designee, using his/her personal login information shall enter data in the e-CRF. The monitor, using his/her personal login information shall verify all critical data points against the source documents and issue electronic queries for the authorised clinical site personnel to respond.

After the monitor has done the source document verification and obtained satisfactory answers to eventual queries from the site, a full quality control (QC) will be performed on the monitored data throughout the clinical investigation by the designated data management (DM) team and queries issued where needed. This process will be repeated until the end of the clinical investigation to allow for a lock of the database for statistical analysis.

A CRF section shall be considered complete when all data are completed, verified by the monitor, data cleaning completed, all outstanding queries resolved, pages frozen and signed off by the principal investigator. Only then can the database be locked and ready for statistical analyses.

11.1 Confidentiality

Patient confidentiality will be maintained throughout the clinical study to the extent required by law. Every attempt will be made to remove patient identifiers from clinical study documents and eCRFs. For this purpose, a unique patient identification code will be assigned and used to allow identification of all

data reported for each patient. This will also ensure that the information can be traced back to the source data.

Study data may be made available to third parties, e.g., in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed, to the extent permitted by law. The identity of a patient will never be disclosed if study data are published.

The Sponsor requires that the study sites comply with the patient confidentiality provisions of the Health Insurance Portability and Accountability Act (HIPAA) issued by the U.S. Department of Health and Human Services (HHS). Sites should maintain patient privacy in accordance to federal regulations (45 CFR Parts 160 and 164), local regulations, and institutional requirements.

11.2 Source Documents

IDE regulations (21 CFR 812) and GCPs require that the Investigator maintain information in the subject's medical records that corroborates data collected on the eCRFs. Throughout the clinical trial duration, the sites' investigators will maintain complete and accurate documentation including but not limited to medical records, clinical trial progress records, laboratory reports, electronic case report forms, signed informed consent forms, device accountability records, correspondence with the IRB and clinical trial monitor or sponsor, adverse event reports, and information regarding patient discontinuation or completion of the clinical trial/investigation. Any source documentation (procedure reports, imaging studies, lab reports, death certificates, etc.) that is sent to the sponsor or reviewing committees should have all patient identifiers removed and replaced with the patient number. To comply with these regulatory requirements/GCP the following information should be included in the patient record at a minimum and if applicable to the investigation:

- Medical history/physical condition of the patient before involvement in the trial sufficient to verify Clinical Investigational Plan entry criteria
- Dated and signed notes on the day of entry into the trial referencing the sponsor, Clinical Investigational Plan number, patient ID number and a statement that informed consent was obtained
- Dated and signed notes from each patient visit (for specific results of procedures and exams)
- Adverse events reported and their resolution including supporting documents such as discharge summaries, ECGs, and lab results including documentation of site awareness of SAEs and of investigator device relationship assessment of SAEs
- Study required laboratory reports and 12-lead ECGs, signed and dated for review and annotated for clinical significance of out of range results
- Notes regarding Clinical Investigational Plan-required and prescription medications taken during the trial (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the trial
- Any other data required to substantiate data entered into the CRF

11.3 Case Report Forms

Primary data collection based on source-documents or clinic chart reviews will be performed clearly and accurately by site personnel trained on the Clinical Investigational Plan and eCRF completion. eCRF data will be collected for all enrolled patients.

11.4 Record Retention

The sponsor will archive and retain all documents pertaining to the trial per the applicable regulatory record retention requirements. The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical trial/investigation records.

All documentation pertaining to the study will be kept by Artegraft or their designee in accordance with ICH guidelines and US FDA regulations.

The investigator will maintain a study file, which should be used to file the IFU, protocol, and device accountability records; correspondence with the IRB and Artegraft; and other study-related documents. The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating subjects, medical records, study-specific source documents, source worksheets, all original signed and dated informed consent forms, query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and Artegraft or its designees.

The investigator shall retain records required to be maintained under this part for a period of 5 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 5 years after the investigation is discontinued. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the sponsor.

In addition, the investigator must make provision for the subject's medical records to be kept for the same period. No data should be destroyed without the agreement of Artegraft. Artegraft will inform the investigator in writing when the trial-related records are no longer needed. Subject's medical records and other original data will be archived in accordance with the archiving regulations or facilities of the study site.

12.0 STUDY MONITORING, AUDITING, AND INSPECTING

IQVIA BioTech will be managing the trial and will provide statistical management. IQVIA BioTech has assisted Artegraft in preparation of the full Trial Protocol. Trial oversight will be by Artegraft, Inc. via periodic audit.

12.1 Study Monitoring Plan

It is the responsibility of the investigator to ensure that the study is conducted in accordance with the protocol, GCP, applicable regulatory requirements, and the currently approved Declaration of Helsinki, and that valid data are entered in the CRF.

To achieve this objective, the monitor's duties are to aid the investigator and, at the same time, the sponsor, in the maintenance of complete, legible, well-organized, and easily retrievable data. The monitor will review the protocol with the investigator. In addition, the monitor will explain the investigator's reporting responsibilities and all applicable regulations concerning the clinical evaluation of the IP.

The investigator will permit representatives of Artegraft and the CRO to monitor the study as frequently as Artegraft or the CRO deem necessary to determine that data recording and protocol adherence are satisfactory. The CRF data and related source documents will be reviewed in detail by the monitor at each visit, in accordance with relevant SOPs and ICH GCP regulations. This includes results of tests performed as a requirement for participation in this study and any other medical records required to confirm information contained in the CRF such as past medical history and secondary diagnoses. The investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

12.2 Auditing and Inspecting

Clinical Investigation sites and clinical investigation documentation may be subject to quality assurance audits during the clinical investigation. In addition, inspections may be conducted by EC/IRBs or regulatory bodies at their discretion, during and after clinical investigation completion.

13.0 REFERENCES

1. US Renal Data System: 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2009.
2. Fresenius Medical Care: Fresenius Medical Care Annual Report 2011—Dialysis Market, Bad Homburg, Germany, Fresenius Medical Care, 2011.
3. US Renal Data System: 2012 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2012.
4. US Renal Data System: 2014 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2014.
5. Manns B, Tonelli M, Yilmaz S, Lee H, Laupland K, Klarenbach S, Radkevich V, Murphy B. Establishment and maintenance of vascular access in incident hemodialysis patients: a prospective cost analysis. *J Am Soc Nephrol* 2005;16(1):201-9.
6. Pastan S, Soucie JM, McClellan WM. Vascular access and increased risk of death among hemodialysis patients. *Kidney Int* 2002;62(2):620-6.
7. Vascular Access Work Group. National Kidney Foundation KDOQI clinical practice guidelines for vascular access. Guideline 7: prevention and treatment of catheter and port complications. *Am J Kidney Dis* 2006; 48(1 suppl 1):S248-57.
8. Goetz AM, Wagener MM, Miller JM, Muder RR. Risk of Infection Due to Central Venous Catheters: Effect of Site of Placement and Catheter Type. *Infect Control Hosp Epidemiol* 1998; Vol. 19, pp. 842-845.
9. Malas MB, Canner JK, Hicks CW, Arhuidese IJ, Zarkowsky DS, Qazi U, Schneider EB, Black 3rd JH, Segev DL, Freischlag JA. Trends in Incident Hemodialysis Access and Mortality. *JAMA Surg*. 2015.
10. Flores IG, Ronces VR, Exaire E, Hernandez CA, Gomez de los Rios J. Venous autologous graft for hemodialysis (original technic). Preliminary report. *Arch Inst Cardiol Mex* 1969;39(2):259-266.
11. Baker LD Jr, Johnson JM, Goldfarb D. Expanded Polytetrafluoroethylene (PTFE) Subcutaneous Arteriovenous Conduit: An Improved Vascular Access for Chronic Hemodialysis. *Am Soc Artif Int Organs* 1976; 22: 382-385.
12. Rosenberg N, Henderson J, Lord GH, Bothwell JW. An arterial prosthesis of heterologous vascular origin. *JAMA*. 1964;187: 741-743.
13. Chinitz JL, Tokoyama T, Bower R, Swartz C. Self-sealing prosthesis for arteriovenous fistula in man. *Trans Am Soc Artif Intern Organs*. 1972;18(0):452-427
14. Merickel JH, Anderson RC, Knutson R et al. Bovine carotid artery shunts in vascular access surgery. *Arch Surg*. 1974;109(2):245-250.
15. Kennealey, P, Elias, N, Hertl, M, et al. A prospective, randomized comparison of bovine carotid artery and expanded polytetrafluoroethylene for permanent hemodialysis vascular access. *Journal of Vascular Surgery*. 2011; 53(6): 1640-1648.
16. Arhuidese, I, Reifsnyder, T, Karim, O. et al. Bovine carotid artery biologic graft outperforms expanded polytetrafluoroethylene for hemodialysis access. *Journal of Vascular Surgery*. 2017; 65: 775-82.

17. Shakarchi, J, Houston, G, Inston, N. Early cannulation grafts for haemodialysis: a systematic review. *J Vasc Access 2015*; 16 (6): 493-497.
18. Shakarchi J, Inston N. Timing of cannulation of arterial grafts: are we too cautious. *Clin Kidney J*, 2015 Jun; 8(3): 290-292.
19. Rosenberg N, Gaughran RI, Henderson J et al. The Use of Segmental Arterial Implants Prepared by Enzymatic Modification of Heterologous Blood Vessels. *Surg Forum*. 1956; Vol VI:242-245.
20. Zilla P, Bezuidenhout D, Human P. Prosthetic vascular grafts: Wrong models, wrong questions, and no healing. *eBiomaterials*. 2007;(28):5009 5027.
21. Katzman HE, Schild AF, Vanderwerf BA. Bovine artegraft arteriovenous fistulas for hemodialysis in one-hundred patients after "conventional" arteriovenous fistulas failed. *Vasc Surg*. 1976; 10(3): 169-75.
22. Johnson, J, Kenoyer, M, Johnson, K, et al. The Modified Bovine Heterograft in Vascular Access for Chronic Hemodialysis. *Ann. Surg*. 1976; 183(1): 62-66.
23. Rosenberg, N, Thompson, JE, Keshishian, JM, Vander Werf, BA. The modified bovine arterial graft. *Arch Surg*. 1976;111 (3):222–226.
24. Mahajan A, Abdoli S, Han SM, Ochoa, CJ, Poster, Early Access of Bovine Carotid Artery Graft can Eliminate the Use of Tunneled Hemodialysis Catheters. CiDA Meeting, 2016.
25. Mahajan A, Abdoli S, Han SM, Ochoa, CJ, Abstract. Early Access of Bovine Carotid Artery Graft can Eliminate the Use of Tunneled Hemodialysis Catheters. *J Vasc Surg*. 2016 63(6)(suppl);, 190S-191S.
26. Mahajan A, Abdoli S, Han SM, Ochoa, CJ, Presentation: Early Access of Bovine Carotid Artery Graft Can Eliminate the Use of Tunneled Hemodialysis Catheters. 31st Annual Mtg of the Western Vascular Society, 2016.
27. Anderson, C, Sicard, G, Etheredge, E. Bovine Carotid Artery and Expanded Polytetrafluroethylene Grafts for Hemodialysis Vascular Access. *Journal of Surgical Research*. 1980; 29: 184- 188.
28. Tellis, V, Kohlberg, W, Bhat, D, et al. Expanded Polytetrafluoroethylene Graft Fistula for Chronic Hemodialysis. *Ann. Surg*. 1979; 189(1): 101-105.
29. Anderson, C, Odand, M, Richardson, C. Renewed Interest in Bovine Heterograft for Vascular Access: A Comparison Between Polytetrafluoroethylene and Bovine. Abstract Presented at the Ninth Biennial Symposium on Dialysis Access Vascular Access for Hemodialysis IX Symposium. May 6-7, 2004. Lake Buena Vista, FL.
30. Butler, H, Baker, L, Johnson, J. Vascular Access for Chronic Hemodialysis: Polytetrafluoroethylene (PTFE) versus Bovine Heterograft. Am J Surgery 1977; 134: 791-793.
31. Sidawy AN, Gray R, Besarab A et al. Recommended standards for reports dealing with arteriovenous hemodialysis accesses. *J Vasc Surg*. 35: 603–610, 2002.
32. Haimov M and Jacobson JH. Experience with the Modified Bovine Arterial Heterograft in Peripheral Vascular Reconstruction and Vascular Access for Hemodialysis. *Ann. Surg*. 1964 Vol. 180 [3]: 291-295.
33. Harlander-Locke M, Jimenez JC, Lawrence PF et al. Bovine Carotid Artery (Artegraft) as a Hemodialysis Access Conduit in Patients Who Are Poor Candidates for Native Arteriovenous Fistulae. *Vascular and Endovascular Surgery*. 2014, Vol. 48(7-8) 497-502.
34. Pineda DM, Dougherty MJ, Wismer MC et al. Bovine carotid artery xenografts for hemodialysis access. *J Vasc. Surg*. 2017 65:1729-1734.
35. Abdoli S, Mahajan A, Han SM et al. Early cannulation of bovine carotid artery grafts (Artegraft) after primary vascular access and fistula revision procedures. Vasc. Surg. 2018: 1-7.

36. https://www.artegraft.com/wp-content/uploads/2018/06/AGI-1616-Cannulation-Wall-Chart.pdf
37. https://player.vimeo.com/video/239902848

14.0 APPENDICES

Appendix 1 - Abbreviations

Abbreviations	Definitions
ADE	Adverse device effects
AE	Adverse event
AV	Arteriovenous
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
BCA	Bovine carotid artery (graft)
BEACH	Bovine Early Access, Compatibility and Hemostasis
CFR	Code of Federal Regulations
CKD	Chronic kidney disease
CRF	Case report form
CVC	Central venous catheter
CRO	Contract research organization
DM	Data management
ECG	Electrocardiogram
EDC	Electronic data capture
eCRF	Electronic case report form
ePTFE	Expanded polytetrafluoroethylene
ESRD	End-stage renal disease
FDA	Food and Drug Administration
GCP	Good clinical practices
HD	Hemodialysis
HIT	Heparin-induced thrombocytopenia
ICF	Informed consent form
ICH	International Council for Harmonisation
IDE	Investigational device exemption
IEC	Independent Ethics Committee
IFU	Instructions for Use

IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
MACE	Major adverse clinical events
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New drug application
NYHA	New York Heart Association
PMA	Pre-market approval
PTFE	Polytetrafluoroethylene
QC	Quality control
SAE	Serious adverse event
SoA	Schedule of Assessments
TPLC	Total product life cycle

Appendix 2 - Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
    - Applicable ICH Good Clinical Practice (GCP) Guidelines.
    - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IFU, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to patients.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
    - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures.
    - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. The study will not start at any study center at which the Investigator has not signed the protocol.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

Insurance

Sponsor will provide insurance, if required, in accordance with local guidelines and requirements. The terms of the insurance will be kept in the study files.

Informed Consent Process

- The Informed Consent must contain details of the study and the potential risks to the patient. It must be written in plain English at an 8th-grade reading level. If patients who do not speak English are expected to be part of the study, then the ICF must be translated into expected languages (e.g., Spanish).

- The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study center.
- The medical record must include a statement that written informed consent was obtained before the patient was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients will be re-consented if the study design changes or if required by the IRB.
- A copy of the ICF(s) must be provided to the patient or the subject's legally authorized representative.

Data Protection

- Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Administrative Structure

Table 11: Study Administrative Structure

Function	Responsible Organization
Study Operations Management; Medical Monitoring	IQVIA BioTech
Study Master File	IQVIA BioTech
Randomization Code	IQVIA BioTech
Data Management	IQVIA BioTech
Clinical Supply Management	Artegraft
Quality Assurance Auditing	Artegraft
Biostatistics	IQVIA BioTech
Medical Writing	IQVIA BioTech
Safety Monitoring (see Section 10.4)	IQVIA BioTech

Medical Monitor

Mark Tulchinskiy, MD, MBA
Senior Medical Director
IQVIA BioTech, Morrisville, North Carolina

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the FDA a summary of the results of the clinical study within 1 year from the end of the clinical study.

Data Quality Assurance

- All patient data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study center personnel are accurate, complete, and verifiable from source

documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for (15) years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Study Center Closure

The Sponsor designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of patients by the Investigator.
- Discontinuation of further study device development.

Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study center data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 3 - Clinical Laboratory Tests

The tests detailed in **Table 11** may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 12: Protocol-required Laboratory Assessments

Laboratory Assessments	**Parameters**
Hematology	Prothrombin Time INR (coagulation) Platelet Count Red Blood Cell (RBC) Count Hemoglobin Hematocrit RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes White Blood Cell Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Blood Urea Nitrogen Creatinine Sodium Potassium Hemoglobin A1C Alkaline phosphatase Total Protein Glucose; non-fasting ALT AST Total Bilirubin
Other Screening Tests	Human chorionic gonadotropin (hCG) serum pregnancy test (for women of childbearing potential)
The results of each test must be entered into the (e)CRF.	

Appendix 4 - Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AEs for Medical Devices

Adverse Device Effect
An AE related to the use of an investigational medical device is classified as an adverse device effect (ADE). Note 1: This definition includes AEs resulting from insufficient or inadequate IFU, deployment, implantation, installation, operation, or any device malfunction of the investigational medical device. This definition includes any event resulting from the use error or intentional misuse of the investigational medical device.

Adverse Event
Any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including an abnormal laboratory finding) in patients, users or other persons whether or not related to the investigational medical device. This includes events related to the investigational medical device or the comparator. This includes events related to the procedures involved. For users or other persons this is restricted to events related to the investigational medical device.

Serious Adverse Event / Serious Adverse Device Effect
An AE that: led to a death, led to a serious deterioration in the health of the patient user or other persons that either resulted in: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function. 5) led to fetal distress, fetal death or a congenital abnormality or birth defect A planned hospitalization for pre-existing condition or a procedure required by the protocol without a serious deterioration in health is not considered to be an SAE

Unexpected Serious Adverse Device Effect
Unexpected serious adverse device effect (USADE) refers to any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unexpected serious problem associated with a device that relates to the rights, safety, or welfare of patients.

Recording and Follow-up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the CRF. Each event must be recorded separately. The IRB and Sponsor should also be notified of each SAE. • It is not acceptable for the Investigator to send photocopies of the subject's medical records to Sponsor, IRB or the CRO in lieu of completion of the Sponsor or the CRO/AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by Sponsor or the CRO. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to Sponsor or the CRO. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Adverse events will be graded as follows:

- Grade 1 (Mild): Events require minimal or no treatment and do not interfere with the patient's daily activities
- Grade 2 (Moderate): Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Grade 3 (Severe): Events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Assessment of Relationship
The likely relationship of each AE to the investigational medical device will be assessed according to the definitions below: **Not related**

Assessment of Relationship

The relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- discontinuation of medical device application or reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure) does not impact on the serious event;
- the event involves a body site, or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
- harm to the patient is not clearly due to use error.

To establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Unlikely related

The relationship to use of the device seems not relevant or the event can be reasonably explained by another cause, but additional information may be obtained.

Possibly Related

The relationship to use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases in which relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probably related

The relationship to use of the investigational device seems relevant or the event cannot reasonably be explained by another cause, but additional information may be obtained.

Causal relationship

The serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;

Assessment of Relationship

Causal relationship continued

- the event involves a body-site or organ that
  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;
  - the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the patient is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

To establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated or as requested by the Sponsor or the CRO to elucidate the nature and cause of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- (If a patient dies during participation in the study or during a follow-up period, the Investigator will provide the CRO or Sponsor with a copy of any postmortem findings including histopathology.)
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor, IRB or CRO within 24 hours of receipt of the information.

Action Taken

- None
- Treatment required
- Hospitalization
- Patient withdrawn
- Administration of study therapy temporarily interrupted
- Administration of study therapy permanently discontinued
- Other (specify)

Outcome

- Recovered, with sequelae
- Recovered, without sequelae
- Improved
- Ongoing
- Death
- Lost to follow-up

Reporting of SAEs

SAE Reporting to Sponsor or the CRO via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Sponsor or the CRO will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the study center will use the paper SAE data collection tool (see next section). • The study center will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given study center, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a study center receives a report of a new SAE from a patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study center can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
SAE Reporting via Paper CRF
• Facsimile transmission of the SAE paper CRF is a secondary method to transmit this information to the medical monitor. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • The Medical Monitor is the contact for SAE reporting.

All SAEs will be forwarded to the independent assessor within 72 hours of receipt by Artegraft. The assessor has the discretion to convene a teleconference at any time to discuss the safety of the Artegraft and may recommend modification or termination of ongoing studies. The assessor or the clinical monitor will inform the Sponsor and IRB of any SAE.

Appendix 5 - Medical Device Malfunctions: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all Sponsor medical devices provided for use in the study (see Section 7.5) for the list of Sponsor medical devices).

Medical Device Incident Definition

- A medical device incident is any device malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other person or to a serious deterioration in his/her state of health.
- Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened.
  AND
- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness.
- Permanent impairment of body function or permanent damage to body structure.
- Condition necessitating medical or surgical intervention to prevent 1 of the above.
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

Examples of Incidents

- A patient, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A subject's study device is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A subject's health deteriorates due to medical device failure.

Documenting Medical device malfunctions

Medical Device Incident Documenting

- Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the Investigator's normal clinical practice, and on the appropriate form of the CRF.
- For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 4.

- The CRF will be completed as thoroughly as possible and signed by the Investigator before transmittal to the Sponsor or designee.
- It is very important that the Investigator provides his/her assessment of causality (relationship to the medical device provided by the Sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

Appendix 6 - Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located on the title page.

Amendment V1.1: 18Feb2019		
Section # and Name	**Description of Change**	**Brief Rationale**
3.3.1: Risk Mitigation	Added methods of control / mitigation	Per FDA request
6.0: Patient Selection & Withdrawal	Clarified patient selection language	Per FDA request
7.7: Training to Use Investigational Device	Clarified text concerning training of dialysis staff	Per FDA request
9.2.1: Overview of Statistical Analysis	Clarified that descriptive statistics will be performed	Per FDA request
Multiple sections	Deleted reference to consenting patients for up to one year	Per FDA request
Appendix 7	Updated the Investigator Agreement to include all required elements	Per FDA request
Amendment V1.2: 25Feb2019		
Section # and Name	**Description of Change**	**Brief Rationale**
Multiple sections	Changed to indicate that patients randomized to the early access group not cannulated in the <72 hour period will still be followed for 30 days after first cannulation.	Per FDA Request
7.7: Training to Use Investigational Device	Clarified text concerning training of dialysis staff	Per FDA Request
13: References	Added two references	Included training material references
Amendment V1.3: 14Mar2019		
Multiple sections	Late access group will be contacted at 6 months and accessed for patency	Per FDA Suggestion
Section 7.6	Method of assigning patients changed	Per FDA Suggestion
Section 9.1	Sample size determination changed	Per FDA Suggestion
Appendix 2, Table 10	Updated Administrative Structure	To reflect current structure
Multiple Sections	Changed Novella Clinical to IQVIA BioTech	CRO changed name

Amendment V2.0: 29Apr2019		
Title Page	Corrected spelling of Medical Monitors last name	Typo correction
Section titles for 8.3 through 8.6	Amended section titles to be consistent with the heading in Table 1: Schedule of Events	Administrative correction to align SOE headers with protocol narrative
Appendix 2	Amended the statement that patients will be re-consented if the study design changes or if required by the IRB	To clarify re-consenting guidance
Amendment V3.0: 20May2019		
Table 1	Added clinical chemistry lab test to the screening schedule of assessments	Administrative correction to include lab tests needed to confirm exclusion criteria
Section 8.1	Added Clinical chemistry lab test to the screening study procedures	Administrative correction to include lab tests needed to confirm exclusion criteria
Appendix 3, Table 11	Added ALT, AST and total bilirubin to the clinical chemistry lab tests	Administrative correction to include lab tests needed to confirm exclusion criteria
Amendment V4.0:21Jun2019		
Section # and Name	**Description of Change**	**Brief Rationale**
Title Page	Corrected the IDE number from G19033 to G190033	Typo correction
Multiple Sections	Change 26 weeks to 6 months, 52 weeks to 12 months	Administrative correction
Table 1	Replaced Table 1 with Table 1a and Table 1b. Table 1a reflects SoA for early access patients, Table 1b reflects SoA for late access and early access drop out patients	To provide more clarity in the schedule of assessments for the different patient populations
Section 6.0	Removed: Any patients that are in the early access group that are not cannulated within 72 hours shall be removed from the study. Replaced with: Any patients that are in the early access group that are not cannulated within 72 hours shall be replaced by additional patients using	Administrative correction to align with intent of protocol

	the randomization plan until the 50-patient number is reached.	
Section 6.7	Expected Enrollment period changed to 3-6 months	Gave range to enrollment period
Section 6.7.2	Enrollment period changed to 3-6 months	To be consistent
Section 6.7.2	Artegraft will monitor trial after 12 months	Limited Data required during extended follow-up so Artegraft will gather data
Section 6.9	Enrollment period changed to 3-6 months	To be Consistent
Section 7.7	"If required" added	Since Artegrafts are commonly commercially available and have a 45 year clinical use history, device training will not be provided except as required. Training materials are available on the web site
Section 7.14	Changed to be consistent with Exclusion Criteria #17	To be consistent
Section 10.2.2	Removed reference to investigational new drug safety reports	Not applicable to medical devices
Section 10.2.7.3	Added the process for submitting a device malfunction to the Sponsor. Removed the bullet indicating that SAE's would be reported the same way.	The instructions were not complete. SAE reporting is not included in this section.
Section 11	Removed references to images	Images will not be captured in the eCRF

Appendix 7 - Investigator Agreement

1. Name and address of Investigator
Name of Principal Investigator
Address
City
State/Province/Region Country ZIP or Postal Code

2. EDUCATION, TRAINING, AND RELEVANT EXPERIENCE (INCLUDING DATES, LOCATION, EXTENT, AND TYPE OF EXPERIENCE) THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE USE UNDER INVESTIGATION
[ ] Curriculum Vitae
[ ] Other Statement of Qualification

3. NAME AND ADDRESS OF EACH MEDICAL SCHOOL, HOSPITAL, RESEARCH FACILITY, OR OTHER SITE WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED	
Location #1	
Location #2	
Location #3	
Location #4	

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE CLINICAL INVESTIGATION. (IF APPLICABLE)	
Location #1	
Location #2	
Location #3	
Location #4	

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) OR ETHICS COMMITTEE (EC) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY
Name of IRB /EC
Address
City
State/Province/Region Country ZIP or Postal Code

6. NAMES OF THE SUBINVESTIGATORS (E.G., RESEARCH FELLOWS, RESIDENTS, ASSOCIATES) WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S)
7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IDENTIFYING THE STUDY TO BE CONDUCTED BY THE INVESTIGATOR
PROTOCOL NO: ARTCT.BEACH.001 Bovine Early Access, Compatibility and Hemostasis Trial Post-Market Study to Evaluate the Safety and Effectiveness of Early Access in Patients Who Require Segmental Arterial Replacement using the Artegraft® Collagen Vascular Graft™
8. HAVE YOU EVER BEEN DISQUALIFIED AS AN INVESTIGATOR BY THE U.S. FOOD AND DRUG ADMINISTRATION?
[ ] No [ ] Yes If yes, please explain:
9. HAVE YOU EVER BEEN INVOLVED IN AN INVESTIGATION OR OTHER RESEARCH THAT WAS TERMINATED?
[ ] No [ ] Yes If yes, please explain:
10. COMMITMENTS
I agree to conduct the study in accordance with the relevant, current investigation plan and applicable regulations of the FDA and any conditions of approval imposed by my reviewing Institutional Review Board (IRB). I agree to abide by all of the responsibilities of Investigators addressed under 21 CFR Part 812, Subpart E and Subpart G. I will only make changes in a protocol after notifying the Sponsor, except when necessary to protect the safety, the rights, or welfare of subjects. I agree to personally conduct or supervise the described investigation(s) on human subjects and will allow only those physician co-investigators listed in this agreement to administer devices and/or perform follow-up medical evaluations. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting the above commitments.

I agree to inform any patients, or any persons used as controls, that the test articles are investigational, and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and Institutional Review Board (IRB) review and approval in 21 CFR Part 56 are met, if applicable.

I agree to report to the Sponsor or designee adverse experiences that occur in the course of the investigation(s) in accordance with the applicable governmental regulations.

I have read and understand the information in the Investigator's Brochure or Instructions for Use (if applicable); including the potential risks of the test articles.

I agree to maintain adequate and accurate records in accordance with government regulations and to make those records available for inspection. I will submit completed protocol case report forms, progress reports, and a final report to the Sponsor or designee at the time frames specified in the Protocol and/or FDA regulations.

If IRB review of the clinical investigation is required, I will ensure that the IRB complies with governmental requirements and will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

As required by 21 CFR Part 54, I will disclose sufficient and accurate financial information to the Sponsor or designee by completing a Financial Disclosure form. I will also notify the Sponsor or designee if my disclosed financial information changes at any time during the clinical investigation or up to one year following the closure of the study.

I agree to comply with all other requirements regarding the obligation of clinical investigators and all other pertinent requirements of the sponsor and government agencies.

11. INSTRUCTIONS FOR COMPLETING STATEMENT OF INVESTIGATOR

- Complete all sections. Attach a separate page if additional space is needed.
- Attach curriculum vitae or other statement of qualifications as described in Section 2.
- Sign and date below.
- Forward the completed form and attachments to the Sponsor or designee.
- Sign and attach a copy of the protocol signature page.

12. SIGNATURE

(Principal Investigator Signature)	(Type or Print Name)	Date (ddMMMyyyy)