A PHASE 3, RANDOMIZED, MULTICENTER, SINGLE-BLIND CONTROLLED STUDY EVALUATING ARTERIOVENOUS FISTULA OUTCOMES WITH AND WITHOUT A PERIVASCULAR SIROLIMUS-ELUTING COLLAGEN IMPLANT (THE ACCESS TRIAL)

Protocol No.:	VT-304
Investigational Product:	Sirolimus-eluting Collagen Implant
Sponsor:	Vascular Therapies, Inc. 105 Union Avenue Cresskill, NJ 07626
Medical Monitor:	Maria DeVita, MD
CRO:	CTI Clinical Trial and Consulting Services, Inc.
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Date of Version:	22-Jan-2018
Version:	Version 5.3

2. SYNOPSIS

Name of Sponsor:
Vascular Therapies, Inc.

Name of Investigational Product:
Sirolimus-eluting Collagen Implant (SeCI)

Name of Active Ingredient:
Sirolimus

Title of Study:
A Phase 3, Randomized, Multicenter, Single-blind, Controlled Study evaluating Arteriovenous fistula outcomes with and without a Perivascular Sirolimus-eluting Collagen Implant (The ACCESS Trial)

Study center(s):
Approximately 20 centers in the United States will participate in this study.

Studied period (years):	**Phase of development:**
Estimated date first patient enrolled: 01 Nov 2015 Estimated date last patient completed: 30 Jun 2019	3

Study Objectives and Hypothesis:
The objective of this study is to evaluate efficacy and safety outcomes following use of the Sirolimus-eluting Collagen Implant in subjects undergoing surgical creation of an AV fistula for vascular access (index procedure). Following successful creation of the AV fistula, the cohort randomized to the treatment group will receive the SeCI; the control group will not receive an implant. The primary study hypothesis is that the proportion of subjects that meet requirements for fistula suitability for dialysis, six months following the index procedure, will be higher in the treatment group in comparison to the control group.

Methodology:
This is a randomized, single blind, multicenter study designed to evaluate the efficacy and safety of the SeCI in subjects who are on hemodialysis or are preparing for hemodialysis and are undergoing surgery for creation of a new AV fistula. Subjects will be randomized 1:1 to the treatment group or control group. Subjects randomized to the treatment group will receive the investigational product; subjects randomized to the control group will undergo AV fistula surgery without implantation of the investigational product. Randomization will be stratified by surgeon and fistula location (radiocephalic or brachiocephalic); at least 80% of the randomized subjects will receive a radiocephalic fistula and at most 20% of the subjects will receive a brachiocephalic fistula. The randomization scheme will be monitored and controlled via the IVR/IWR system.

The first subject enrolled by each participating surgeon will be a “run-in subject”, not part of the randomized subject set. “Run-in subjects” will undergo surgery for the creation of an AV fistula and receive the SeCI. This is to familiarize the investigators with the SeCI implant procedure. Enrolled subjects will be followed for a period of one year from the time of their index procedure.

Number of patients (planned):
Planned enrollment is approximately 240 subjects. Approximately 220 subjects are planned to be randomized in equal proportions to treatment and control to yield approximately 200 evaluable subjects. The randomized cohort will include a minimum of 100 evaluable subjects who are on hemodialysis at the

time of the index procedure.

In addition to the 220 randomized subjects, approximately 20 run-in subjects will be enrolled.

Diagnosis and main criteria for inclusion:

Subjects of either gender, at least 18 years of age and undergoing a planned creation of a single-stage radiocephalic or brachiocephalic, end-to-side fistula are eligible to participate in this study. All subjects must meet inclusion/exclusion criteria prior to enrollment in the study.

Inclusion Criteria:

Subjects must meet ALL of the following inclusion criteria to be enrolled in the study:

1. Age of at least 18 years
2. Provide written informed consent using a form that is approved by the Institutional Review Board (IRB)
3. Currently on hemodialysis for ≤12 months or expected to initiate hemodialysis within approximately 6 months of the creation of the AV fistula.
4. Life expectancy of at least one year
5. Vascular anatomy suitable for creation of the AV fistula, determined by pre-procedure duplex ultrasound (target artery ≥2 mm, target vein ≥2.5 mm, and vein depth ≤5 mm in the cannulation segment, the latter approximately 10 cm in length)
6. Successful creation of a single-stage radiocephalic or brachiocephalic end-to-side fistula
7. Willing to comply with the specified follow-up evaluations

Exclusion Criteria:

Subjects will be excluded if ANY of the following exclusion criteria apply:

1. Pregnant, breastfeeding, or plans to be pregnant during the course of the study
2. Prior AV access created on the limb where the fistula surgery is planned
3. History of steal syndrome from a previous hemodialysis vascular access requiring intervention or access abandonment
4. ST-elevation MI or cerebrovascular accident within 30 days of the index procedure
5. Known hypersensitivity to the following: sirolimus, beef or bovine collagen
6. Hypotension with systolic blood pressures <100 mm Hg at the time of screening
7. Receiving anticoagulant therapy for non-cardiac indications
8. Currently on immunosuppressive medication(s)
9. Known or suspected active infection at the time of the AV fistula surgery
10. Known to be HIV positive
11. Presence of a medical condition, which, in the Investigator's opinion, may interfere with the subject's optimal participation in the study (e.g., malignancy or undergoing chemotherapy or radiation treatments)
12. Known advanced liver disease with decompensated cirrhosis, jaundice, ascites or bleeding varices
13. Prisoner, mentally incompetent, and/or current alcohol or drug abuser
14. Currently participating in another investigational study

Investigational product, dosage and mode of administration:

- Test Product: Sirolimus-eluting Collagen Implant (SeCI)
- Dose: Each implanted product will consist of two component membranes, an anastomosis component (AF) and a venous component (VF). The 3 cm^2 anastomosis component will contain a nominal sirolimus dose of 225 μg. The venous component (selection based on the diameter and the length of

the exposed vein) will contain a nominal sirolimus dose of 225 µg (3 cm^2), 300 µg (4 cm^2), 337.5 µg (4.5 cm^2), or 450 µg (6 cm^2). Depending on the combined size of the two implanted membranes, the resulting nominal sirolimus dose will be 450 µg (total implant planar area = 6 cm^2), 525 µg (total implant planar area = 7 cm^2), 562.5µg (total implant planar area = 7.5 cm^2), or 675 µg (total implant planar area = 9 cm^2).

- Mode of Administration: Perivascular implant

Duration of treatment:

Single-use, intra-operative implant.

Reference therapy, dosage and mode of administration:

No reference therapy will be employed in this study. Subjects randomized to the control group will undergo surgery for creation of an AV fistula without the SeCI.

Criteria for Evaluation:

Efficacy:

The primary endpoint of the study is **Fistula Suitability for Dialysis at 6 months (FSD6)** defined as a composite of:

a. For subjects who are on hemodialysis by day 150, suitability for dialysis will be determined by the ability to use the fistula for dialysis using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min for at least two-thirds of the dialysis sessions performed during a 30 day suitability ascertainment period that will commence on day 150.

b. For subjects who are not on hemodialysis on day of enrollment and who do not initiate hemodialysis by day 150, suitability for dialysis will be determined by a vascular ultrasound performed at the 6 month follow up visit. Suitability for dialysis will be defined as a fistula with an access vein diameter (AVD) of ≥6 mm (internal diameter) and an access blood flow of ≥500 mL/min.

Secondary Endpoints

1. **Fistula Suitability for Dialysis at 12 months** defined as a composite of:
   a. For subjects who are on hemodialysis by day 330, suitability for dialysis will be determined by the ability to use the fistula for dialysis using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min for at least two-thirds of the dialysis sessions performed during a 30 day suitability ascertainment period that will commence on day 330.
   b. For subjects who are not on hemodialysis on day of enrollment and who do not initiate hemodialysis by day 330, suitability for dialysis will be determined by a vascular ultrasound performed at the 12 month follow up visit. Suitability for dialysis will be defined as a fistula with an access vein diameter (AVD) of ≥6 mm (internal diameter) and an access blood flow of ≥500 mL/min.
2. **Fistula Maturation by Day 90** defined as a composite of:
   a. For subjects who are on hemodialysis by day 90:
      – Three consecutive dialysis sessions using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min, the first of these three dialysis sessions completed on or before 90 days from the time of creation of the AV fistula, or
      – Two-needle dialysis on or before 90 days, with no further use of the catheter prior to achieving three consecutive dialysis sessions using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min.
   b. For subjects who do not initiate hemodialysis by day 90, fistula access vein diameter (AVD) of ≥6 mm (internal diameter) and an access blood flow of ≥500 mL/min determined by a

vascular ultrasound performed at the 3-month follow up visit.

3. **Secondary Patency**, defined as the interval from the time of access placement until access abandonment.
4. **Re-intervention Rate**, defined as the total number of vascular access interventions performed during study participation to maintain or re-establish patency of the index fistula, as well as interventions to assist fistula maturation divided by the total subject participation time in the study.

Tertiary Endpoints

1. Time To First Dialysis (TTFD) defined as the time from fistula creation to the time when the fistula can support three consecutive dialysis sessions using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min. TTFD will be evaluated in subjects who are on hemodialysis at the time of study enrollment or initiate hemodialysis within 28 days of the index procedure.
2. Fistula Suitability for Dialysis at 6 months with preserved primary patency defined as a composite of:
    a. For subjects who are on hemodialysis by day 150, suitability for dialysis will be determined by the ability to use the fistula for dialysis using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min for at least two-thirds of the dialysis sessions performed during a 30 day suitability ascertainment period that will commence on day 150
    b. For subjects who are not on hemodialysis on day of enrollment and who do not initiate hemodialysis by day 150, suitability for dialysis will be determined by a vascular ultrasound performed at the 6 month follow up visit. Suitability for dialysis will be defined as a fistula with an access vein diameter (AVD) of ≥6 mm (internal diameter) and an access blood flow of ≥500 mL/min
3. Fistula Suitability for Dialysis at 12 months with preserved primary patency
4. Primary Patency, defined as the interval from the time of fistula creation until the first occurrence of fistula thrombosis or an intervention performed to restore/maintain patency.

Safety:

Safety evaluations will be based on treatment emergent adverse events (TEAEs) up to the 2 month visit and vascular access events reported during study participation. Treatment emergent is defined as any adverse event that emerges after the subject is enrolled (run-in and randomized) in the study. The run-in subjects' adverse events will be included in the safety evaluation. Vascular access events include access dysfunction, thrombosis, access-related hand ischemia, infiltration requiring a rest period, fistula-related bleeding, infection, problems with wound healing, aneurysm, pseudoaneurysm, and all interventional procedures performed on the study fistula. During follow-up, up to the 2 month visit, all AEs and concomitant medications will be recorded. After the 2 month visit, the following will be reported and recorded: vascular access events, concomitant medications and therapies associated with vascular access, serious adverse events (SAEs) and AEs reported during an SAE.

An independent Data and Safety Monitoring Board (DSMB) will periodically review safety data.

Data Analysis and Statistical methods:

The data will be summarized in tables by treatment group, and will list the mean, standard deviation, median, minimum, maximum, and number of subjects in a group for continuous data; count and percentage for categorical data; and median, 25^{th} and 75^{th} percentiles, relative risk and 95% confidence intervals for time-to-event data. Data will be listed for each subject. Statistical analyses will be performed and data appendices will be created using SAS.

The efficacy analysis will be conducted on the full analysis set. The full analysis set will consist of all randomized subjects who received vascular access surgery (***NOTE: The run-in patient at each site will be excluded from the full analysis set but will be included in the safety set***). The primary efficacy endpoint is Fistula Suitability for Dialysis at 6 months (FSD6) This endpoint will be analyzed using logistic regression with factors for treatment and stratum. The treatment effect will be tested at overall

alpha=0.05, 2-sided, to compare the proportions of patients between treatments.

Time to event secondary endpoints will be analyzed via stratified log rank test. Binary endpoints will be compared between treatments via the same logistic regression model as for the primary endpoint. Continuous secondary endpoints will be compared via analysis of covariance for a model including treatment, strata, and baseline covariate if measured at baseline, or non-parametric rank tests if normality or homogeneity assumptions appear substantially violated. Endpoints will be tested for statistically significant difference between treatments, each at alpha=0.05, 2-sided.

Summary statistics for demographics and important baseline parameters will be provided by treatment group and for all subjects combined. TEAE's and SAE's will be summarized by counts and proportions by treatment for each body system organ class and by preferred term within class.

Power and Sample Size Considerations

All power calculations are via EAST® 6.4. Assuming the TRUE underlying FSD6 rates are 45% for control and 76% for treatment (based on Phase 2 data), the sample size of N=200 patients contributing to the analysis has >99% power to yield a statistically significant (alpha=0.05 2-sided) difference between treatments. Allowing for uncertainty in the Phase 2 data, if the TRUE underlying FSD6 rates are 45% and 65%, N=200 has approximately 82% power.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialized terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADR	Adverse Drug Reaction
AE	Adverse event
AF	Anastomotic component of the Sirolimus-eluting Collagen Implant
ASA	Acetylsalicylic acid, Aspirin
AV	Arteriovenous
CFD	Complication Free Days
CFR	Code of Federal Regulations
CKD	Chronic Kidney Disease
CRO	Contract Research Organization
DAC	Dialysis Access Consortium
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
ESRD	End Stage Renal Disease
FSD6	Fistula Suitability for Dialysis
GCP	Good Clinical Practice
HEENT	Head, Eyes, Ears, Nose and Throat
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IP	Investigational Product
IRB	Institutional Review Board
IVR System	Interactive Voice Response System
IWR System	Interactive Web Response System
KDQOL-SF	Kidney Disease and Quality of Life Short Form survey
MI	Myocardial infarction
PI	Principal Investigator
P.O.	Per OS (oral administration)

Abbreviation or Specialist Term	Explanation
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SeCI	Sirolimus-eluting Collagen Implant
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File
TTFD	Time to First Dialysis
USRDS	United States Renal Data System
VF	Venous Component of the Sirolimus-eluting Collagen Implant

5. INTRODUCTION

5.1. Background

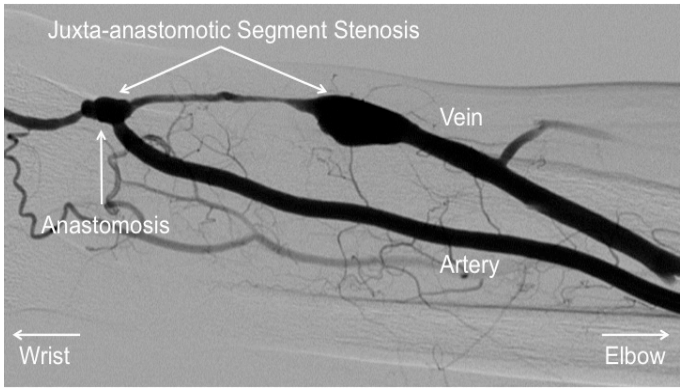
Hemodialysis represents the most common form of renal replacement therapy for patients with End-Stage Renal Disease (ESRD). Since successful hemodialysis requires a repeated, reliable and durable access to the circulation, a functional vascular access is a lifeline for this patient population and a critical and actionable determinant of mortality and morbidity.

A ***mature AV fistula*** is the preferred vascular access for hemodialysis because compared to the alternatives of AV grafts and catheters, an AV fistula has substantially lower thrombosis and infection rates, as well as decreased health care related expenditures. These advantages are reflected in clinical practice guidelines and also explain the rationale underlying the Centers for Medicare and Medicaid Services' "Fistula First Initiative".

Unfortunately, in contemporary practice, on average, approximately 50% of AV fistulae never develop to the point of being suitable for hemodialysis, and those that do, often take up to five months or more to mature [1-6]. Fistula maturation is the process of dilatation and thickening of the anastomosed blood vessels – a consequence of changes in pressure and blood flow. Although dilatation and wall thickening have to occur in both artery and vein, venous dilatation is the clinically more apparent process in fistula maturation and ultimately determines fistula suitability for dialysis. The most common finding related to AV fistula maturation failure is juxta-anastomotic segment (JAS) stenosis, starting at or around the anastomosis and extending for a variable distance along the outflow vein (Figure 1) [7-14].

In 2007, Roy Chaudhury and colleagues published results from histological, morphometric, and immuno-histochemical analysis of tissue samples obtained from stenotic venous segments from patients with early AV fistula failure [10]. They showed significant luminal stenosis, primarily as a result of eccentric neointimal hyperplasia, a manifestation of the blood vessel tissue response to injury and healing. A recent prospective randomized study [7] reported that a flow limiting stenosis located at and around the juxta-anastomotic segment was responsible for failure to mature in ~ 50% of the cases.

Figure 1: Dysfunctional AV Fistula



The etiology of neointimal hyperplasia is likely multifactorial and includes trauma, vascular manipulation related to surgery, as well as altered shear stress, i.e., exposing the low-flow, low-pressure venous conduit to high arterial pressures and flow [9,11,13].

Vascular access continues to be the weakest link in maintenance hemodialysis, with access complications being the leading cause for hospitalization among ESRD patients. Of particular concern are hospitalizations for infection in the hemodialysis population, which have increased 43% since 1993 [15].

5.2. Unmet Clinical Need

The lack of a therapeutic solution to correct the problem of fistula non-maturation defines a huge, well-recognized, unmet clinical need since in the absence of a functional fistula, patients dialyze with a catheter. All the stakeholders involved in the care of the patient with ESRD are aligned and in agreement that there is an urgent need to find a solution to the problem. Specifically what is needed is:

1. A reduction in time to fistula maturation as well as an increase in the proportion of fistulae that mature and become suitable for cannulation for first dialysis. The sooner the newly constructed fistula is functionally ready to support dialysis, the less the dependence on catheters.
2. Ensuring that the fistula maintains functionality without need for supplementary interventions. Currently, supplementary interventions are performed with the intent of assisting the fistula to become suitable for dialysis and/or maintain functional patency. These additional interventions have variable levels of success in the short term but negatively impact long term durability [16-18].

The status quo will continue until such time a therapeutic solution to the problem of fistula non-maturation and reduced suitability for dialysis becomes available. The investigational product that is being tested in the clinical trial seeks to provide this solution and bridge this unmet need.

5.3. Rationale for Evaluating the Sirolimus-eluting Collagen Implant

Sirolimus (Rapamycin), marketed under the trade name Rapamune® for the prevention of organ rejection in patients with a kidney transplant, has shown clinically useful anti-restenotic properties in coronary arteries [19-22]. Sirolimus has a unique dual mechanism of action involving both anti-inflammatory and cytostatic anti-proliferative effects resulting from inhibition of a signal transduction kinase, the mammalian target of rapamycin (mTOR) [23]. When delivered locally to the vascular wall from a stent platform, sirolimus suppresses neointimal hyperplasia. This therapeutic effect has translated into a clinically meaningful reduction in the incidence of in-stent restenosis [24-28].

Local perivascular delivery of sirolimus using the Sirolimus-eluting Collagen Implant (SeCI) at the time of AV fistula creation is expected to inhibit neointimal proliferation at the local

treatment sites thereby reducing the risk of a flow limiting stenosis. In turn, this is expected to improve fistula maturation and suitability for dialysis with preserved primary patency.

5.4. Rationale for the Study Endpoints

In the United States, over 80% of all ESRD patients initiate dialysis with a catheter and approximately 50% are still utilizing a catheter after 90 days [15]; hence, the sooner the newly constructed fistula is functionally ready to support dialysis, the less the dependence on catheters.

The single largest vascular access related contributor to mortality and morbidity is related to catheter use. Catheter complications result from lower dialysis dose, missed/shorter dialysis sessions, central vein stenosis and occlusions (which besides contributing to highly morbid situations like superior vena cava syndrome, prevent creation of an access on the ipsilateral side) and most importantly from infections and septicemia.

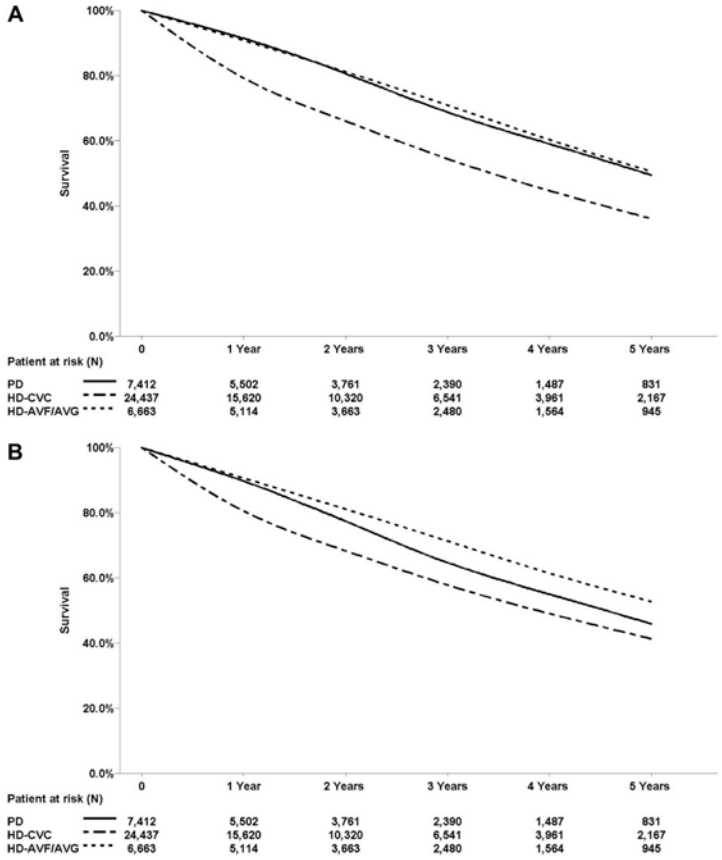
In 2013, Ravani and colleagues reported the results of a meta-analysis of 67 cohort studies comprising 586,337 participants [29]. The primary outcome of the analysis was all cause mortality; secondary outcomes included fatal and non-fatal cardiovascular events, fatal and non-fatal infections and all cause hospitalizations. The relative risks (catheter vs. AV fistula) for these various metrics are shown in Table 3.

Table 3: Summary of Absolute Risks Associated with Vascular Access Types (Catheter vs. Fistula)

Cause (Number of Patients)	RR (95% CI)
All cause mortality (N=411,068)	1.53 (1.41-1.67)
Fatal infections (N=229,824)	2.12 (1.79-2.52)
Non Fatal Infections (N=14,947)	4.66 (2.63-8.26)
Cardiovascular Events (N=232,236)	1.38 (1.24-1.54)
Hospital Admissions (N=54,660)	1.68 (1.33-2.12)

In a registry-based, observational, cohort study, Perl et al. compared the outcomes of 40,526 incident dialysis patients who were registered between 2001 and 2008 to those of 7,412 peritoneal dialysis patients. One year mortality was similar for the 6,663 patients on hemodialysis using an AV fistula or graft but was 80% higher for the 24,437 hemodialysis patients dialyzing with a catheter (adjusted HR, 1.8; 95% confidence intervals [CI], 1.6 to 1.9) Figure 2 [30].

Figure 2: Survival curves for Hemodialysis-CVC (short-dashed line), Hemodialysis-AV fistula/AV graft (long-dashed line), and Peritoneal Dialysis (solid line)



Survival curves demonstrate higher 1-year mortality in HD-CVC patients. (A) Unadjusted. (B) Adjusted on the basis of a stratified Cox proportional Hazards model stratified by HD-CVC, PD, and HD-AVF/AVG and adjusted for age, race, gender, era of dialysis initiation, end-stage renal disease comorbidity index, primary renal diagnosis, serum albumin, eGFR, province of treatment, and late referral.

Central line–associated blood stream infections (CLABSIs) are an important subset of health-care associated infections, and affect approximately 5% of patients hospitalized in the United States each year. In an effort to focus on the growing problem of CLABSIs within the hemodialysis patient population, the CDC published national estimates of the number of CLABSIs among patients in intensive-care units (ICUs), inpatient wards and outpatient hemodialysis facilities for calendar years 2008 and 2009 (Table 4) [31].

Table 4: Estimated Annual Number of CLABSIs by Health-care Setting and Year

Health-care Setting	Year	No. of Infections (Upper and Lower Bound of Sensitivity Analysis)
Intensive-care units	2001 2009	43,000 (27,000–67,000) 18,000 (12,000–28,000)
Inpatient wards	2009	23,000 (15,000–37,000)
Outpatient hemodialysis[a]	2008	37,000 (23,000–57,000)

[a] Case definitions approximate current definition of CLABSI according to the National Healthcare Safety Network

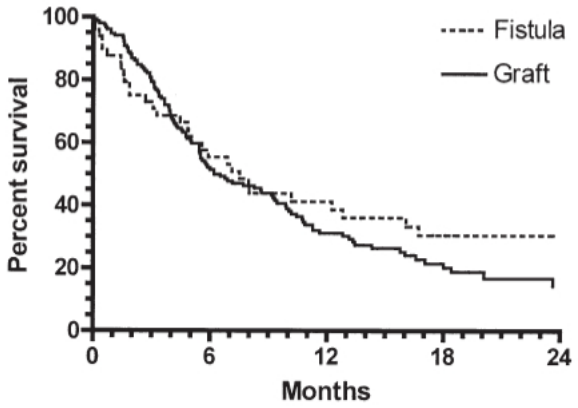
This CDC report from 2011 highlighted the following:

1. Whereas in 2001, the number one cause of CLABSI in the United States was a patient in the ICU, this was no longer the case eight years later. In 2009, an estimated 25,000 fewer CLABSIs occurred among patients in ICUs in comparison to 2001 (a 58% reduction).
2. The reported mortality risk from CLABSIs is 12-25%; hence, these reductions represent an estimated savings of 3,000–6,000 lives and reduction in health-care costs of $414 million in ICUs in 2009 alone [32].
3. Today in the United States, the majority of CLABSIs are occurring outside of ICUs, many outside of hospitals altogether, especially in outpatient dialysis clinics.
4. The substantial number of estimated CLABSIs among hemodialysis patients (more than 40,000/year) emphasizes another important prevention priority because these infections are a major cause of hospital admissions and mortality [33].

Delays and failures of the fistula becoming suitable for dialysis prolongs catheter dependence and increases the unfavorable downstream consequences of catheter use [29,34-36].

Preserving fistula functionality at 6 and 12 months addresses the issue of fistula durability, the primary goal of vascular access creation. At the present time, if follow up clinical evaluations, often supported by duplex ultrasound studies, suggests fistula non-maturation or fistula dysfunction is a result of a flow limiting stenosis, a supplementary intervention is performed – most often a balloon angioplasty to dilate and treat anastomotic and/or venous segment stenosis [37,38]. Hence, these supplementary interventions are performed with the intent of assisting the fistula to become suitable for dialysis and/or maintain functional patency. Although in the short term, in a variable proportion of fistulae these additional intervention(s) are successful in their intent [16], in the longer term, these additional procedures negatively impact durability (Figure 3; Table 5) [17,18]. The most plausible explanation for this reduced durability is that the vascular trauma related to the interventional procedure itself fuels an aggressive neointimal response resulting in recurrent stenosis [17].

Figure 3: Intervention-free Access Survival after Angioplasty



Analysis was restricted to the first angioplasty for each patient. P=0.36 by log-rank test for the comparison between the 2 survival curves [18].

Table 5: Cumulative AV Fistula Survival Based on Number of Interventions Required for Fistula Suitability for Dialysis

No of Interventions required for Fistula Suitability for Dialysis →	Zero Interventions	One Intervention	Two or More Interventions
Cumulative AV Fistula Survival at 1-year[a]	92%	78%	68%
Number of Interventions per Year after AV fistula Cannulation	0.76±0.10	1.37±0.31	3.51±2.20

[a] Cumulative access survival as measured from access cannulation to permanent failure.

It is important to emphasize that supplementary interventions are performed in response to a clinical need signaling either lack of fistula maturation or fistula dysfunction. Hence, as long as a therapeutic solution to this unmet clinical need is unavailable (the negative connotations of additional procedures notwithstanding), the clinical relevance of these supplementary interventions cannot be diminished. Conversely, the therapeutic solution to address the problem of fistula non-maturation being evaluated in the clinical trial is expected to reduce or eliminate the need for supplementary interventions. Maintaining patency without the need for additional interventions manifests as preserved primary patency and is one clinical measure of the effect of the study drug. Reducing or altogether eliminating the need for supplementary interventions is very beneficial to patients (by providing freedom from procedure related pain and morbidity and avoiding interruption of dialysis schedules), to the fistula (by preserving its durability) and to dialysis providers and payors.

5.5. Summary

Providing a functional AV fistula by shortening time to first dialysis and ensuring its durability, i.e., ensuring suitability of the fistula for dialysis at later time points is vital for ESRD patients on dialysis. The current standard of care is unable to provide a solution to the problem of fistula non-maturation, setting the stage for a huge, well acknowledged unmet clinical need. Stated differently, fistula maturation is the most critical event in the natural history of an AV fistula and maximizing the proportion of fistula that become suitable for cannulation for first dialysis and remain useful for dialysis (i.e., maintain functionality) continues to be high priority goals in vascular access. Fistula suitability for dialysis should occur not only without assistance of supplementary procedures, it should also occur early - typically within 6 weeks of surgical fistula creation. The timing is important since a functional fistula triggers end of catheter dependence reducing the risk of catheter related complications, which are substantial.

The clinical importance and rationale of the study endpoints are summarized in Table 6.

Table 6: Relevance of Study Endpoints

Metric	Implication	Comment
Reducing time to first dialysis using the fistula	Fistula maturation[a], signaling functionality is a critical event Reduces catheter dependence	Catheter use for hemodialysis increases mortality and morbidity
Maintaining a higher proportion of fistulae suitable for dialysis at 6 months	Addresses durability of the mature functional fistula	Approximately 50% of all AV fistulae are not suitable for hemodialysis
Fistula with and without preserved primary patency	Supplementary interventions impact fistula durability	Patient morbidity Multiple interventions Adequacy of dialysis Health care costs

[a] Lack of a solution to the problem of fistula non-maturation defines the unmet clinical need

6. STUDY ENDPOINTS AND OBJECTIVE

The objective of this study is to evaluate efficacy and safety outcomes following use of the Sirolimus-eluting Collagen Implant in subjects undergoing surgical creation of an AV fistula for vascular access (index procedure). Following successful creation of the AV fistula, the cohort randomized to the treatment group will receive the SeCI; the control group will not receive an implant.

The primary study hypothesis is that the proportion of subjects that meet fistula suitability for dialysis six months following the index procedure, will be higher in the treatment group in comparison to the control group.

6.1. Primary Endpoint

The primary endpoint of the study is **Fistula Suitability for Dialysis at 6 months (FSD6)** defined as a composite of:

a. For subjects who are on hemodialysis by day 150, suitability for dialysis will be determined by the ability to use the fistula for dialysis using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min for at least two-thirds of the dialysis sessions performed during a 30 day suitability ascertainment period that will commence on day 150.
b. For subjects who are not on hemodialysis on day of enrollment and who do not initiate hemodialysis by day 150, suitability for dialysis will be determined by a vascular ultrasound performed at the 6 month follow up visit. Suitability for dialysis will be defined as a fistula with an access vein diameter (AVD) of ≥6 mm (internal diameter) and an access blood flow of ≥500 mL/min.

6.2. Secondary Endpoints

The secondary endpoints of the study are:

1. Fistula Suitability for Dialysis at 12 months defined as a composite of:
    a. For subjects who are on hemodialysis by day 330, suitability for dialysis will be determined by the ability to use the fistula for dialysis using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min for at least two-thirds of the dialysis sessions performed during a 30 day suitability ascertainment period that will commence on day 330.
    b. For subjects who are not on hemodialysis on day of enrollment and who do not initiate hemodialysis by day 330, suitability for dialysis will be determined by a vascular ultrasound performed at the 12 month follow up visit. Suitability for dialysis will be defined as a fistula with an access vein diameter (AVD) of ≥6 mm (internal diameter) and an access blood flow of ≥500 mL/min.
2. Fistula Maturation by Day 90 defined as defined as a composite of:
    a. For subjects who are on hemodialysis by day 90:
        – Three consecutive dialysis sessions using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min, the first of these three dialysis sessions completed on or before 90 days from the time of creation of the AV fistula, or
        – Two-needle dialysis on or before 90 days with no further use of the catheter prior to achieving three consecutive dialysis sessions using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min.
    b. For subjects who do not initiate hemodialysis by day 90, fistula access vein diameter (AVD) of ≥6 mm (internal diameter) and an access blood flow of ≥500 mL/min determined by a vascular ultrasound performed at the 3-month follow up visit.
3. Secondary Patency, defined as the interval from the time of access placement until access abandonment.
4. Re-intervention Rate, defined as the total number of vascular access interventions performed during study participation to maintain or re-establish patency of the index fistula, as well as interventions to assist fistula maturation divided by the total subject participation time in the study.

6.3. Tertiary Endpoints

The tertiary endpoints of the study are:

1. Time To First Dialysis (TTFD) defined as the time from fistula creation to the time when the fistula can support three consecutive dialysis sessions using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min. TTFD will be evaluated in subjects who

are on dialysis at the time of study enrollment or initiate dialysis within 28 days of the index procedure.

2. Fistula Suitability for Dialysis at 6 months with preserved primary patency defined as a composite of:
   a. For subjects who are on hemodialysis by day 150, suitability for dialysis will be determined by the ability to use the fistula for dialysis using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min for at least two-thirds of the dialysis sessions performed during a 30 day suitability ascertainment period that will commence on day 150
   b. For subjects who are not on hemodialysis on day of enrollment and who do not initiate hemodialysis by day 150, suitability for dialysis will be determined by a vascular ultrasound performed at the 6 month follow up visit. Suitability for dialysis will be defined as a fistula with an access vein diameter (AVD) of ≥6 mm (internal diameter) and an access blood flow of ≥500 mL/min
3. Fistula Suitability for Dialysis at 12 months with preserved primary patency
4. Primary Patency, defined as the interval from the time of fistula creation until the first occurrence of fistula thrombosis or an intervention performed to restore/maintain patency.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 3, multicenter, randomized, single blind, controlled, adaptive study designed to evaluate the efficacy and safety of the use of the Sirolimus-eluting Collagen Implant (SeCI) in subjects who are on hemodialysis or are preparing for hemodialysis and are undergoing surgical creation of an AV fistula in comparison to subjects who do not receive the implant.

Subjects of either gender, who are at least 18 years of age, undergoing hemodialysis or are expected to initiate hemodialysis within 6 months of study enrollment, and require a new single-stage radiocephalic or brachiocephalic end-to-side fistula will be eligible to participate in this study. It is expected that all subjects will be enrolled across approximately 20 sites and each enrolled subject will be followed for one year from the time of fistula creation.

Subjects who meet eligibility criteria and undergo successful AV fistula creation will be eligible for enrollment. The study plans to enroll approximately 240 subjects. Of these, the first subject enrolled by a participating surgeon will be a run-in subject; run-in subjects will not be part of the randomized set; all run-in subjects will receive the SeCI. The intent of enrolling run-in subjects in the clinical study is to familiarize the investigators with the implant procedure. Approximately 220 subjects will be randomized in a 1:1 ratio using permuted block randomization stratified by surgeon and fistula location (radiocephalic or brachiocephalic) to yield approximately 200 evaluable subjects. The randomized cohort will include a minimum of 100 evaluable subjects who are on hemodialysis at the time of the index procedure.

Subjects who are on hemodialysis at the time of enrollment will undergo evaluations to determine fistula suitability for cannulation starting no earlier than day 28 post index procedure; the frequency of assessments for cannulation suitability will be at the discretion of the investigator and/or designee. The decision to proceed with first cannulation will be made by the investigator based on clinical assessment of the fistula. In addition, subjects who have not initiated hemodialysis by:

- Day 90 post index procedure, and the index fistula has not been abandoned, a vascular ultrasound will be performed at the 3 month follow up visit,
- Day 150 post index procedure, and the index fistula has not been abandoned, a vascular ultrasound will be performed at the 6 month follow up visit, and
- Day 330 post index procedure, and the index fistula has not been abandoned, a vascular ultrasound will be performed at the 12 month follow up visit.

An intervention to assist fistula maturation is not permitted in the study prior to 42 days following the index procedure. However, an intervention, if deemed necessary, is permitted upon diagnosis of one or more of the following events:

1. Access thrombosis
2. Access-related hand ischemia
3. High output cardiac failure
4. Access infiltration or AV fistula-related bleeding
5. Access-related infection/wound complication
6. Aneurysm and pseudoaneurysm

All enrolled subjects will be followed for a period of one year from the time of their index procedure.

7.2. Schedule of Events

A schedule of events/assessments is provided Table 7.

Table 7: Schedule of Events

	Baseline	**Index Proc.**	**1W Visit[a]**	**2W Visit**	**3W Visit[a]**	**4W Visit**	**5W Visit[a]**	**6W Visit**	**2M Visit**	**3M Visit**	**6M Visit**	**9M Visit**	**End of Study Visit**
	-45d	**0d**	**+7±2d**	**+15±2d**	**+21±2d**	**+28±2d**	**+35±2d**	**+42±2d**	**+60±4d**	**+90±4d**	**+180 ±15d**	**+270 ±15d**	**+360 ±15d**
Informed consent	X												
Patient demographics	X												
Medical and medication history[b]	X												
Physical exam	X												X
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments[d]	X								X		X		X
Dialysis adequacy data[e]	X								X		X		X
Pregnancy test[f]	X												
Access planning	X												
Index procedure		X											
Eligibility assessment		X											
Randomization		X											
Access assessment[g]		X	X	X	X	X	X	X	X	X	X	X	X
Clinical examination[h]		X		X		X		X					
Cannulation assessment[i]						X							
Vascular ultrasound										X[j]	X[k]		X[l]

	Baseline	Index Proc.	1W Visit[a]	2W Visit	3W Visit[a]	4W Visit	5W Visit[a]	6W Visit	2M Visit	3M Visit	6M Visit	9M Visit	End of Study Visit
	-45d	**0d**	**+7±2d**	**+15±2d**	**+21±2d**	**+28±2d**	**+35±2d**	**+42±2d**	**+60±4d**	**+90±4d**	**+180 ±15d**	**+270 ±15d**	**+360 ±15d**
Adverse events		X	X	X	X	X	X	X	X	X[m]	X[m]	X[m]	X[m]
Concomitant medications		X	X	X	X	X	X	X	X	X[m]	X[m]	X[m]	X[m]
KDQOL Survey	X					X				X	X		X

[a] This visit is applicable to subjects who are undergoing hemodialysis at the time of the visit.
[b] Medical history should include the subject's vascular access history (prior AV accesses and catheters) including number of interventions (e.g., number of angioplasties, thrombectomies, etc.) over the previous 6months.
[c] For subjects on hemodialysis, vital sign values will be obtained from the dialysis session records.
[d] Laboratory values will be obtained from the local medical records; the assays will not be performed centrally and should be the most recent available relative to the visit.
[e] Dialysis adequacy data should be collected for subjects undergoing hemodialysis at the time of the scheduled visit.
[f] A pregnancy test should be performed within 7 days prior to the index procedure for women with childbearing potential.
[g] Access assessment to document fistula patency and fistula development status. Evaluations include thrill and bruit assessment, arm elevation test, and augmentation test. Access assessments should be performed by delegated dialysis unit personnel.
[h] Clinical exam to document wound healing, any local problems such as infection, wound dehiscence, unexpected amount of arm swelling, etc., and evaluation for presence of steal syndrome (e.g. pain in digits, discoloration, cold fingers, blue fingers, etc.).
[i] For subjects on hemodialysis at the time of enrollment or subjects who initiate dialysis within 28 days of index procedure, cannulation assessment will start no earlier than 28 days post index procedure with subsequent assessments occurring at discretion of the investigator and/or designee. The decision to proceed with first cannulation will be based on the investigator's clinical assessment.
[j] For subjects who do not initiate hemodialysis by Day 90 and the index fistula has not been abandoned, a duplex ultrasound must be performed at the 3 month follow up visit.
[k] For subjects whose index fistula is not in use for hemodialysis on day 150 and the index fistula has not been abandoned, a duplex ultrasound must be performed at the 6 month follow up visit.
[l] For subjects whose index fistula is not in use for hemodialysis on day 330 and the index fistula has not been abandoned, a duplex ultrasound must be performed at the 12 month follow up visit.
[m] Record adverse events and concomitant medications that are associated with or occurred during an SAE or vascular access events. See sections 9.7 and 12.

7.3. Subject Visits

7.3.1. Baseline (-45 days)

Screening assessments must occur within 45 days of the index procedure. Assessments can be performed at any time within the 45 day window unless otherwise indicated below.

Once informed consent has been obtained, a subject will be screened for study participation. The original signed Subject Information and Informed Consent Form (ICF) must be maintained in the subject's source document, with a copy provided to the subject (see Section 16.3).

The following evaluations must be performed:

- Inclusion/exclusion criteria (see Section 8)
- Demographic data (age, gender, race, and ethnicity)
- Medical and medication history. Information on relevant previous and concomitant illnesses, or any clinically significant signs or symptoms discovered as a result of screening procedures will be recorded as medical history. Particular emphasis should be given to etiology of renal failure and co-morbidities like diabetes, hypertension, coronary artery disease, peripheral vascular disease, cerebrovascular disease, congestive heart failure, dyslipidemia, tobacco and alcohol use, allergies, and bleeding history. Medical history should also include the subject's vascular access history including number of interventions (e.g., number of angioplasties, thrombectomies, etc.) over the previous 6 months.
- Vital signs (temperature, heart rate, blood pressure), body weight, and height. Note: If the subject is undergoing hemodialysis, these values should be obtained, post-dialysis, from the most recent hemodialysis session in relation to the scheduled visit. All abnormal vital sign values must be evaluated by the investigator for clinical significance in relation to the subject's underlying condition.
- General physical exam
- Local laboratory assessments
- Dialysis adequacy data, if the subject is undergoing hemodialysis
- Pregnancy test for women with childbearing potential (non-childbearing potential is defined as not having had a menstrual period for 1 year or surgically sterilized). The pregnancy test must be performed within 7 days prior to the index procedure.
- Access planning procedures. Duplex ultrasound of the index limb for vascular mapping to determine diameter and depth of the target outflow vein and diameter of the target artery. In subjects with a history of or current use of a catheter ipsilateral to the side where the AV fistula is planned or a pacemaker has been placed in the ipsilateral central vein, a venogram is ***strongly recommended*** as part of access planning. This approach is consistent with current standard of care.
  Note: Access planning procedures may be performed/repeated on the day of index procedure to verify individual measurements.

- Kidney Disease and Quality of Life – Short Form (KDQOL-SF) survey (see Appendix B)

7.3.2. Index Procedure (0 day)

The following evaluations must be performed prior to enrollment:

- Vital signs (temperature, heart rate, and blood pressure); pre-surgical
- Confirmation of successful AV fistula creation. Successful creation is defined as a patent fistula with satisfactory hemostasis. Successful creation will be determined by the presence of a palpable thrill and any one of the following:
  - a satisfactory auditory signal using a handheld Doppler, or
  - visual augmentation of the juxta-anastomotic segment following application of a proximal tourniquet, or,
  - verification of fistula patency using duplex ultrasound
- ***Should the AV fistula creation procedure fail, the subject will be considered a screen failure and will not be enrolled***.

Subjects designated as run-in patients will receive the SeCI. Randomization is accomplished using the IVR/IWR System. See Section 9.2 for further details.

The following activities must be performed following enrollment and prior to discharge:

- Pre-discharge access assessment (presence of a thrill and bruit) of the AV fistula to document fistula patency
- Assessment of AEs following completion of the index procedure
- Update of concomitant medications

In subjects undergoing hemodialysis at the time of enrollment, the following assessment must be performed at the first dialysis session following subject enrollment:

- Access assessment to document fistula patency and fistula development status. Evaluations include thrill and bruit assessment, arm elevation test, and augmentation test.
  Note: Access assessments should be performed by delegated personnel.

7.3.3. 1 Week Visit (+7±2 days)

This visit is applicable to subjects who are undergoing hemodialysis at the time of the visit. The following evaluations must be performed:

- Vital signs (temperature, heart rate, and blood pressure) and body weight. These values should be obtained, post-dialysis, from the most recent hemodialysis session in relation to the scheduled visit. All abnormal vital sign values must be evaluated by

the investigator for clinical significance in relation to the subject's underlying condition.

- Access assessment to document fistula patency and fistula development status. Evaluations include thrill and bruit assessment, arm elevation test, and augmentation test.
  Note: Access assessments should be performed by delegated personnel.
- Adverse event assessments (see Section 12.2). AE assessments include:
  - Symptoms spontaneously reported by the subject
  - Any examination findings and test results determined by the investigator to be a clinically significant change or abnormality
  - Other information relating to the subject's health becoming known to the investigator (e.g., hospitalization, lab abnormalities, etc.)
  - Vascular access related AEs and interventions (e.g., angioplasty, percutaneous thrombectomy, surgical revision, surgical thrombectomy, declotting, administration of lytics, etc.) since last visit
  - Introduction/creation of a new, alternate access (catheter, AV fistula, or AV graft) since last visit
- Update concomitant medications

7.3.4. 2 Week Visit (+15±2 days)

The following evaluations must be performed:

- Vital signs (temperature, heart rate, and blood pressure) and body weight. Note: If the subject is undergoing hemodialysis, these values should be obtained, post-dialysis, from the most recent hemodialysis session in relation to the scheduled visit. Any abnormal vital sign values must be evaluated by the investigator for clinical significance in relation to the subject's underlying condition.
- Clinical examination of the surgical wound to document wound healing, any local problems such as infection, wound dehiscence, unexpected amount of arm swelling, etc., and evaluation for presence of steal syndrome (e.g. pain in digits, discoloration, cold fingers, blue fingers, etc.).
- Access assessment to document fistula patency and fistula development status. Evaluations include thrill and bruit assessment, arm elevation test, and augmentation test.
  Note: Access assessments should be performed by delegated personnel.
- Adverse event assessments (see Section 12.2). AE assessments include:
  - Symptoms spontaneously reported by the subject

  - Any examination findings and test results determined by the investigator to be a clinically significant change or abnormality
  - Other information relating to the subject's health becoming known to the investigator (e.g., hospitalization, lab abnormalities, etc.)
  - Vascular access related AEs and interventions (e.g., angioplasty, percutaneous thrombectomy, surgical revision, surgical thrombectomy, declotting, administration of lytics, etc.) since last visit
  - Introduction/creation of a new, alternate access (catheter, AV fistula, or AV graft) since last visit
- Update concomitant medications

7.3.5. 3 Week Visit (+21±2 days)

This visit is applicable to subjects who are undergoing hemodialysis at the time of the visit. The following evaluations must be performed:

- Vital signs (temperature, heart rate, and blood pressure) and body weight. These values should be obtained, post-dialysis, from the most recent hemodialysis session in relation to the scheduled visit. All abnormal vital sign values must be evaluated by the investigator for clinical significance in relation to the subject's underlying condition.
- Access assessment to document fistula patency and fistula development status. Evaluations include thrill and bruit assessment, arm elevation test, and augmentation test.
  Note: Access assessments should be performed by delegated personnel.
- Adverse event assessments (see Section 12.2). AE assessments include:
  - Symptoms spontaneously reported by the subject
  - Any examination findings and test results determined by the investigator to be a clinically significant change or abnormality
  - Other information relating to the subject's health becoming known to the investigator (e.g., hospitalization, lab abnormalities, etc.)
  - Vascular access related AEs and interventions (e.g., angioplasty, percutaneous thrombectomy, surgical revision, surgical thrombectomy, declotting, administration of lytics, etc.) since last visit
  - Introduction/creation of a new, alternate access (catheter, AV fistula, or AV graft) since last visit
- Update concomitant medications

7.3.6. 4 Week Visit (+28±2 days)

The following evaluations must be performed:

- Vital signs (temperature, heart rate, and blood pressure) and body weight. Note: If the subject is undergoing hemodialysis, these values should be obtained, post-dialysis, from the most recent hemodialysis session in relation to the scheduled visit. All abnormal vital sign values must be evaluated by the investigator for clinical significance in relation to the subject's underlying condition.
- Clinical examination of the surgical wound to document wound healing, any local problems such as infection, wound dehiscence, unexpected amount of arm swelling, etc., and evaluation for presence of steal syndrome (e.g. pain in digits, discoloration, cold fingers, blue fingers, etc.).
- Access assessment to document fistula patency and fistula development status. Evaluations include thrill and bruit assessment, arm elevation test, and augmentation test.
  Note: Access assessments should be performed by delegated personnel.
- KDQOL-SF survey (see Appendix B).
- Cannulation assessment if the subject is undergoing hemodialysis (see Section 10.1). The first evaluation to determine fistula suitability for cannulation will start no earlier than 28 days from the time of index procedure. The investigator and/or designee will determine the frequency of subsequent assessments for cannulation suitability. The decision for first cannulation will be based on the investigator's clinical assessment of the fistula.
- Adverse event assessments (see Section 12.2). AE assessments include:
  - Symptoms spontaneously reported by the subject
  - Any examination findings and test results determined by the investigator to be a clinically significant change or abnormality
  - Other information relating to the subject's health becoming known to the investigator (e.g., hospitalization, lab abnormalities, etc.)
  - Vascular access related AEs and interventions (e.g., angioplasty, percutaneous thrombectomy, surgical revision, surgical thrombectomy, declotting, administration of lytics, etc.) since last visit
  - Introduction/creation of a new, alternate access (catheter, AV fistula, or AV graft) since last visit
- Update of concomitant medications

7.3.7. 5 Week Visit (+35±2 days)

This visit is applicable to subjects who are undergoing hemodialysis at the time of the visit. The following evaluations must be performed:

- Vital signs (temperature, heart rate, and blood pressure) and body weight. These values should be obtained, post-dialysis, from the most recent hemodialysis session in relation to the scheduled visit. All abnormal vital sign values must be evaluated by the investigator for clinical significance in relation to the subject's underlying condition.
- Access assessment to document fistula patency and fistula development status. Evaluations include thrill and bruit assessment, arm elevation test, and augmentation test.
  Note: Access assessments should be performed by delegated personnel.
- Adverse event assessments (see Section 12.2). AE assessments include:
  - Symptoms spontaneously reported by the subject
  - Any examination findings and test results determined by the investigator to be a clinically significant change or abnormality
  - Other information relating to the subject's health becoming known to the investigator (e.g., hospitalization, lab abnormalities, etc.)
  - Vascular access related AEs and interventions (e.g., angioplasty, percutaneous thrombectomy, surgical revision, surgical thrombectomy, declotting, administration of lytics, etc.) since last visit
  - Introduction/creation of a new, alternate access (catheter, AV fistula, or AV graft) since last visit
- Update concomitant medications

7.3.8. 6 Week Visit (+42±2 days)

The following evaluations must be performed:

- Vital signs (temperature, heart rate, and blood pressure) and body weight.
  Note: If the subject is undergoing hemodialysis, these values should be obtained, post-dialysis, from the most recent hemodialysis session in relation to the scheduled visit. All abnormal vital sign values must be evaluated by the investigator for clinical significance in relation to the subject's underlying condition.
- Clinical examination of the surgical wound to document wound healing, any local problems such as infection, wound dehiscence, unexpected amount of arm swelling, etc., and evaluation for presence of steal syndrome (e.g. pain in digits, discoloration, cold fingers, blue fingers, etc.).
- Access assessment to document fistula patency and fistula development status. Evaluations include thrill and bruit assessment, arm elevation test, and augmentation test.
  Note: Access assessments should be performed by delegated personnel.
- Adverse event assessments (see Section 12.2). AE assessments include:

  - Symptoms spontaneously reported by the subject
  - Any examination findings and test results determined by the investigator to be a clinically significant change or abnormality
  - Other information relating to the subject's health becoming known to the investigator (e.g., hospitalization, lab abnormalities, etc.)
  - Vascular access related AEs and interventions (e.g., angioplasty, percutaneous thrombectomy, surgical revision, surgical thrombectomy, declotting, administration of lytics, etc.) since last visit
  - Introduction/creation of a new, alternate access (catheter, AV fistula, or AV graft) since last visit
- Update concomitant medications

7.3.9. 2 Month Visit (+60±4 days)

The following evaluations must be performed:

- Vital signs (temperature, heart rate, and blood pressure) and body weight. These values should be obtained, post-dialysis, from the most recent hemodialysis session in relation to the scheduled visit. All abnormal vital sign values must be evaluated by the investigator for clinical significance in relation to the subject's underlying condition.
- For subjects whose index fistula is not in use for hemodialysis at the 2 month visit and the index fistula has not been abandoned, access assessment to document fistula patency and fistula development status. Evaluations include thrill and bruit assessment, arm elevation test, and augmentation test.
  Note: Access assessments should be performed by delegated personnel.
- Adverse event assessments (see Section 12.2). AE assessments must include:
  - Symptoms spontaneously reported by the subject
  - Any examination findings and test results determined by the investigator to be a clinically significant change or abnormality
  - Other information relating to the subject's health becoming known to the investigator (e.g., hospitalization, lab abnormalities, etc.)
  - Vascular access related AEs and interventions (e.g., angioplasty, percutaneous thrombectomy, surgical revision, surgical thrombectomy, declotting, administration of lytics, etc.) since last visit
  - Introduction/creation of a new, alternate access (catheter, AV fistula, or AV graft) since last visit
- Update of concomitant medications

- Laboratory assessments. All abnormal laboratory values must be evaluated by the investigator for clinical significance in relation to the subject's underlying condition
- Dialysis adequacy data, if the subject is undergoing hemodialysis

7.3.10. 3 Month Visit (+90±4 days)

The following evaluations must be performed:

- Vital signs (temperature, heart rate, and blood pressure) and body weight. Note: If the subject is undergoing hemodialysis, these values should be obtained, post-dialysis, from the most recent hemodialysis session in relation to the scheduled visit. All abnormal vital sign values must be evaluated by the investigator for clinical significance in relation to the subject's underlying condition.
- For subjects whose index fistula is not in use for hemodialysis at the 3 month visit and the index fistula has not been abandoned
  - Access assessment to document fistula patency and fistula development status. Evaluations include thrill and bruit assessment, arm elevation test, and augmentation test.
    Note: Access assessments should be performed by delegated personnel.
  - A duplex ultrasound must be performed. The ultrasound report should include the cephalic vein diameter and include fistula flow measurements
- KDQOL-SF survey (see Appendix B)
- Adverse event assessments (see Section 12.2). AE assessments include:
  - Vascular access related AEs and interventions (e.g., angioplasty, percutaneous thrombectomy, surgical revision, surgical thrombectomy, declotting, administration of lytics, etc.) since last visit
  - Introduction/creation of a new, alternate access (catheter, AV fistula, or AV graft) since last visit
  - Other information relating to the subject's health becoming known to the investigator (e.g., hospitalization, etc.)
- Update of concomitant medications (See Section 9.7)

7.3.11. 6 Month Visit (+180±15 days)

The following evaluations must be performed:

- Vital signs (temperature, heart rate, and blood pressure) and body weight. Note: If the subject is undergoing hemodialysis, these values should be obtained, post-dialysis, from the most recent hemodialysis session in relation to the scheduled visit. All abnormal vital sign values must be evaluated by the investigator for clinical significance in relation to the subject's underlying condition.

- For subjects whose index fistula is not in use for hemodialysis on day 150 and the index fistula has not been abandoned
  - Access assessment to document fistula patency and fistula development status. Evaluations include thrill and bruit assessment, arm elevation test, and augmentation test.
  - A duplex ultrasound must be performed. The ultrasound report should include the cephalic vein diameter and include fistula flow measurements
- KDQOL-SF survey (see Appendix B)
- Adverse event assessments (see Section 12.2). AE assessments include:
  - Vascular access related AEs and interventions (e.g., angioplasty, percutaneous thrombectomy, surgical revision, surgical thrombectomy, declotting, administration of lytics, etc.) since last visit
  - Introduction/creation of a new, alternate access (catheter, AV fistula, or AV graft) since last visit
  - Other information relating to the subject's health becoming known to the investigator (e.g., hospitalization, etc.)
- Update of concomitant medications (See Section 9.7)
- Laboratory assessments. All abnormal laboratory values must be evaluated by the investigator for clinical significance in relation to the subject's underlying condition.
- Dialysis adequacy data, if the subject is undergoing hemodialysis

7.3.12. 9 Month Visit (+270±15 days)

The following evaluations must be performed:

- Vital signs (temperature, heart rate, and blood pressure) and body weight. Note: If the subject is undergoing hemodialysis, these values should be obtained, post-dialysis, from the most recent hemodialysis session in relation to the scheduled visit. All abnormal vital sign values must be evaluated by the investigator for clinical significance in relation to the subject's underlying condition.
- For subjects whose index fistula is not in use for hemodialysis at the 9 month visit and the index fistula has not been abandoned, access assessment to document fistula patency and fistula development status. Evaluations include thrill and bruit assessment, arm elevation test, and augmentation test.
  Note: Access assessments should be performed by delegated personnel.
- Adverse event assessments (see Section 12.2). AE assessments include:
  - Vascular access related AEs and interventions (e.g., angioplasty, percutaneous thrombectomy, surgical revision, surgical thrombectomy, declotting, administration of lytics, etc.) since last visit

  - Introduction/creation of a new, alternate access (catheter, AV fistula, or AV graft) since last visit
  - Other information relating to the subject's health becoming known to the investigator (e.g., hospitalization, etc.)
- Update of concomitant medications (See Section 9.7)

7.3.13. End of Study Visit (+360±15 days)

The following evaluations must be performed:

- Vital signs (temperature, heart rate, and blood pressure) and body weight. Vital signs should be obtained at the time of the general physical exam. All abnormal vital sign values must be evaluated by the investigator for clinical significance in relation to the subject's underlying condition.
- For subjects whose index fistula is not in use for hemodialysis on day 330 and the index fistula has not been abandoned
  - Access assessment to document fistula patency and fistula development status. Evaluations include thrill and bruit assessment, arm elevation test, and augmentation test.
  - A duplex ultrasound must be performed. The ultrasound report should include the cephalic vein diameter include fistula flow measurements
- KDQOL-SF survey (see Appendix B)
- General physical exam
- Adverse event assessments (see Section 12.2). AE assessments include:
  - Vascular access related AEs and interventions (e.g., angioplasty, percutaneous thrombectomy, surgical revision, surgical thrombectomy, declotting, administration of lytics, etc.) since last visit
  - Introduction/creation of a new, alternate access (catheter, AV fistula, or AV graft) since last visit
  - Other information relating to the subject's health becoming known to the investigator (e.g., hospitalization, etc.)
- Update of concomitant medications (See Section 9.7)
- Laboratory assessments. All abnormal laboratory values must be evaluated by the investigator for clinical significance in relation to the subject's underlying condition.
- Dialysis adequacy data, if the subject is undergoing hemodialysis

8. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects at least 18 years age, of either gender undergoing a planned creation of an upper extremity AV fistula, without known contraindications for use of sirolimus or collagen are eligible to participate in this study. All subjects are to be screened for study participation according to the inclusion and exclusion criteria described below. Every effort will be made to establish a subject's eligibility prior to enrollment. Subjects who meet all inclusion criteria and none of the exclusion criteria will be eligible to participate in the study.

8.1. Inclusion Criteria

Subjects must meet ALL of the following inclusion criteria to be enrolled in the study:

1. Age of at least 18 years
2. Provide written informed consent using a form that is approved by the Institutional Review Board (IRB)
3. Currently on hemodialysis for ≤12 months or expected to initiate hemodialysis within approximately 6 months of the creation of the AV fistula.
4. Life expectancy of at least one year
5. Vascular anatomy suitable for creation of the AV fistula, determined by pre-procedure duplex ultrasound (target artery ≥2 mm, target vein ≥2.5 mm, and vein depth ≤5 mm in the cannulation segment, the latter approximately 10 cm in length)
6. Successful creation of a single-stage radiocephalic or brachiocephalic end-to-side fistula
7. Willing to comply with the specified follow-up evaluations

8.2. Exclusion Criteria

Subjects will be excluded if ANY of the following exclusion criteria apply:

1. Pregnant, breastfeeding, or plans to be pregnant during the course of the study
2. Prior AV access created on the limb where the fistula surgery is planned
3. History of steal syndrome from a previous hemodialysis vascular access requiring intervention or access abandonment
4. ST-elevation MI or cerebrovascular accident within 30 days of the index procedure
5. Known hypersensitivity to the following: sirolimus, beef or bovine collagen
6. Hypotension with systolic blood pressures <100 mm Hg at the time of screening
7. Receiving anticoagulant therapy for non-cardiac indications
8. Currently on immunosuppressive medication(s)
9. Known or suspected active infection at the time of the AV fistula surgery

10. Known to be HIV positive
11. Presence of a medical condition, which, in the Investigator's opinion, may interfere with the subject's optimal participation in the study (e.g., malignancy or undergoing chemotherapy or radiation treatments)
12. Known advanced liver disease with decompensated cirrhosis, jaundice, ascites or bleeding varices
13. Prisoner, mentally incompetent, and/or current alcohol or drug abuser
14. Currently participating in another investigational study

8.3. Withdrawal or Discontinuation

Following randomization, neither the sponsor nor the investigator should discontinue any subject from the study. However, subjects may be discontinued from the clinical study for any of the following reasons:

- Withdrawal of consent by the subject; or
- Lost to follow-up

Although each subject is expected to remain in this study for the duration of follow-up, all subjects have the right to withdraw at any point during the study without prejudice. Withdrawal of consent for follow-up should be accompanied by documentation of the reason for withdrawal. Withdrawal of consent for follow-up visits should be distinguished from withdrawal of consent for non-patient contact follow-up, e.g., medical records checks. Preferably the subject should withdraw consent in writing and, if the subject or the subject's representative refuses or is physically unavailable, the site should document and sign the reason for the subject's failure to withdraw consent in writing. The investigator and/or designee will, if at all possible, complete all End of Study evaluations on subjects who withdraw from the study. If a subject chooses to withdraw from the study because of an adverse event, the subject should be explicitly asked about the contribution of possible adverse events to their decision to withdraw consent; any adverse event information elicited along with the principal specific event and any related test results must be captured in the source document and eCRF. Subjects who discontinue participation in the study due to an adverse event experienced during study conduct will, at minimum, be followed until resolution or until stabilization.

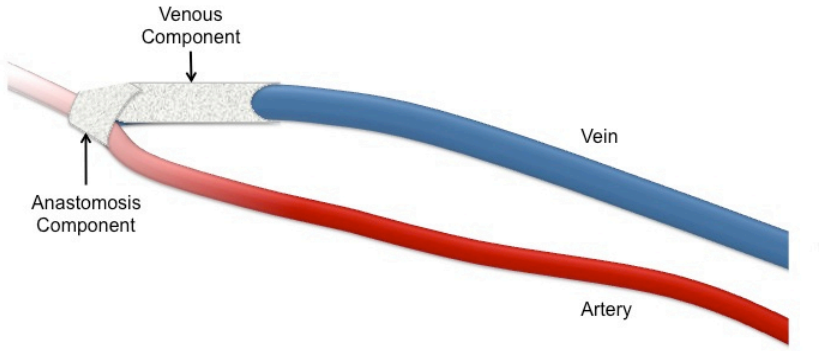
If a subject is lost to follow-up, the investigator and/or designee will make at least 3 phone attempts to reach the subject. If the phone attempts are unsuccessful, the site will mail a certified letter to the subject's last known address requesting they return for evaluation. If a subject dies during the course of the study, they will not be considered withdrawn from the study, but rather no further follow-up will be required. The reason for withdrawal or discontinuation will be documented in the subject's source document and eCRF.

9. TREATMENT OF SUBJECTS

9.1. Description of Investigational Product

The Sirolimus-eluting Collagen Implant is a sterile, bioabsorbable implant comprised of sirolimus at a nominal drug density of 75 µg per cm^2 of implanted collagen membrane. A single implant consists of two component membranes; one anastomosis component (AF) and one outflow vein component (VF) (Figure 4). Following hydration, the membranes will "self-curl" into a cylindrical configuration. This facilitates implantation around the blood vessel without the need for suturing the free edges, avoiding the creation of a potentially restrictive external band.

Figure 4: Product Implantation Scheme



The size of the AF component is 30 x 10 mm (planar surface area of 3 cm^2). The same sized AF component is used for radiocephalic and brachiocephalic fistulae. The selection of the VF component will be guided by intra-operative measurements obtained following successful completion of the construction of the arteriovenous (AV) fistula.

The VF component is wrapped around the outflow vein (juxta-anastomotic segment) starting at the heel of the anastomosis. Since the diameter of the vein as well as the length of the outflow vein mobilized during surgery can vary between patients, four different VF component sizes, appropriate for a range of blood vessel dimensions will be available (planar surface area ranges from 3 cm^2 to 6 cm^2) (Table 8). Selection of the VF component will be based on the outflow vein diameter and length of the outflow vein that has been exposed and mobilized.

Table 8: Description of the Component Membranes

Implant Location	Component Code	Size (mm)[a]	Membrane Planar Surface Area (cm^2)	Sirolimus Content (µg)[b]
Anastomosis	AF3010	30 x 10	3	225
Outflow vein	VF1520	15 x 20	3	225
	VF1530	15 x 30	4.5	337.5
	VF2020	20 x 20	4	300
	VF2030	20 x 30	6	450

[a] Size is expressed as circumference (C) x axial length (L).
[b] Target sirolimus density of 75 µg/cm^2

Depending on the size of the VF component implanted, the nominal sirolimus dose will be 450 µg (total implant area = 6 cm^2), 525 µg (total implant area = 7 cm^2), 562.5 µg (total implant area = 7.5 cm^2), or 675 µg (total implant area = 9 cm^2) (Table 9).

Table 9: Product Matrix and Nominal Sirolimus Dosages

Implant Option	Components	Implant Area (cm^2)	Dose (µg)	Total Implant Area (cm^2)	Total Dose (µg)
A	AF3010 + VF1520	3 + 3	225 + 225	6	450
B	AF3010 + VF2020	3 + 4	225 + 300	7	525
C	AF3010 + VF1530	3 + 4.5	225 + 337.5	7.5	562.5
D	AF3010 + VF2030	3 + 6	225 + 450	9	675

Product implantation instructions are provided in the Instructions For Use (see Appendix C) enclosed with each SeCI component membrane package.

9.2. Subject Enrollment

9.2.1. Index Procedure

The conduct of the AV fistula creation surgery, including type of anesthesia and the surgical technique must be documented. The technical components of the surgery include the type of suture used for the anastomosis, method used to occlude arterial inflow and outflow, etc. ***Hydrostatic distension of the vein and use of rigid dilators to size or probe the vein is permitted, however, balloon dilation of the vein is not permitted***. The immediate pre-operative and intra-operative medications administered as part of the surgical procedure will be documented. These medications include heparin and any topical vasodilators.

Once the surgeon declares patency of the newly constructed fistula and that hemostasis is satisfactory, the surgical outcome is judged to be successful and the subject will be eligible for enrollment in the study. Confirmation of successful AV fistula creation will be determined by the presence of a palpable thrill and any one of the following:

- a satisfactory auditory signal using a handheld Doppler, or
- visual augmentation of the juxta-anastomotic segment following application of a proximal tourniquet, or,
- verification of fistula patency using duplex ultrasound

Should the AV fistula creation procedure fail, the subject will be considered a screen failure.

9.2.2. Treatment Assignment

The designated surgical coordinator will retain control of the investigational product during the conduct of the index procedure. Until use, the investigational product must be kept in a controlled area with limited access and the tamper evident seal must not be broken until treatment assignment.

9.2.2.1. Run-in Subjects

The first subject eligible for enrollment under each participating surgeon at each investigational site in the study will receive the SeCI. The designated surgical study coordinator will break the tamper evident seals, the surgical team will prepare the product per instructions provided in the Instructions for Use (see Appendix C), and the surgeon will implant the investigational product.

9.2.2.2. Randomization

Following successful creation of an AV fistula, subjects will be randomized in a 1:1 ratio to treatment or control using permuted block randomization stratified by surgeon and fistula location (radiocephalic / brachiocephalic). At least 80% of the subjects randomized will receive a radiocephalic fistula and at most 20% of the randomized subjects will receive a brachiocephalic fistula. The above randomization scheme will be applicable to subjects on hemodialysis at the time of enrollment or not on hemodialysis at the time of enrollment separately. The randomization scheme will be monitored and controlled via the IVR/IWR system.

The designated surgical study coordinator will contact the IVR/IWR System to receive the randomization code and treatment assignment for the subject.

- If the subject is randomized to the treatment group, the designated surgical study coordinator will break the tamper evident seals, the surgical team will prepare the product per instructions provided in the Instructions for Use (see Appendix C), and the surgeon will implant the investigational product.
- If the subject is randomized to the control group, the surgeon will complete the surgery per standard practice, (without implanting the investigational product). The designated surgical study coordinator will ensure that the tamper evident seals on the investigational product packaging have not been broken and will return the investigational product to inventory.

Following completion of surgery, the designated surgical study coordinator will confirm using the IVR/IWR System that:

- the surgical procedure was successfully completed, and,
- the randomization number was used

Once a randomization number has been used, it will not be re-used. Authorized study personnel will ensure that the assigned randomization number is recorded in the subject's source document.

Upon completion of the index procedure, the surgical incision will be closed according to the surgeon's standard practice.

If the subject is randomized to the control group, the designated surgical study coordinator will ensure that the tamper evident seal on the component membrane packaging has not been broken and will return the investigational product to inventory.

9.2.3. Blinding/Unblinding

This study is a single-blind investigation since it will not be possible to blind the implanting surgeon, the designated surgical coordinator, operating room staff, and unblinded monitor with respect to the assigned treatment group.

Blinded personnel include but are not limited to the subject, the nephrologist, the staff at the dialysis centers, and the sponsor and/or designee who handle study monitoring, data management, and analysis.

An individual with knowledge of the randomization code/treatment assignment will not exclusively participate in decisions relating to fistula outcomes (e.g., fistula maturation/non-maturation, determination of fistula abandonment, need for supplementary interventions, etc.).

In case of an emergency, when knowledge of the actual treatment becomes medically necessary, a blinded investigator will be able to obtain details of the treatment assigned to an individual subject. The Medical Monitor will be immediately informed that the blind needs to be broken who will then authorize the blind to be broken and treatment assignment disclosed to the blinded investigator. Under no circumstances will the blind be broken prior to notification and consent of the Medical Monitor.

Any direct verbal or written communication regarding treatment identification beyond what is required at an institution for the recording of the surgical procedure is prohibited.

The post-operative note in the hospital chart, the official surgical report, as well as the letter to the referring MD will include the usual description of the AV fistula surgery along with the statement "subject is participating in investigational study protocol VT-304". ***There will be no reference made as to whether the subject received the investigational implant product or not***. The randomization code that was assigned to the subject (without details about the subject's treatment assignment) will also be recorded in the source document.

The unblinded surgical study coordinator will maintain the subject's treatment assignment in an Overall Accountability Log in a secured, controlled area that has restricted access. The carton containing the investigational product will include a 6-part label with space provided for the subject's number, initials and the assigned randomization code. The surgical study coordinator will place this label on the Overall Accountability Log for future accountability. An unblinded monitor will perform the accountability review (see Section 9.5).

9.3. Packaging and Labeling

Each component membrane of the Sirolimus-eluting Collagen Implant is a sterile, single-use only product, packaged in an amber vial, which is stored in a Tyvek pouch. The Tyvek pouch is the primary sterile barrier. The Tyvek pouch is packaged in a foil pouch. The foil pouch is placed within a carton. The product is gamma sterilized and is non-pyrogenic. Each carton contains one (1) component membrane.

Each component of the product (amber vial, foil pouch, and carton) is labeled with the following information: product name, component code, size, lot number, storage conditions, sponsor's identification and address, and the statement, "Caution: New Drug – Limited by Federal (or United States) law to investigational use."

Each package contains a 6-part label, which includes the following information: product name, component code, and lot number. One section should be removed and placed on the appropriate Accountability Log for study product accountability.

9.4. Storage Conditions

The SeCI supply must be stored in the original packaging between 2°C and 8°C (36-46°F) in a secured, controlled area with restricted access.

9.5. Accountability

In accordance with ICH-GCP, the investigational site will account for all investigational supplies throughout the study. Details of receipt, storage, administration, and return of the SeCI will be recorded in an Overall Accountability Log provided by the sponsor and/or designee. The Overall Accountability Log will be maintained by the Surgical Study Coordinator in a secured, controlled area that has restricted access. An unblinded monitor will perform all functions related to drug accountability in order to maintain the blind throughout the study.

9.6. Return and Destruction

After an unblinded monitor has performed final accountability and the investigator and/or designee have reconciled any discrepancies, all unused investigational supply will be returned to the sponsor. Documentation of the returned investigational supply will accompany the shipment and a copy will be kept at the site. The site will not destroy any used or unused investigational supply unless the sponsor provides written authorization to the contrary.

In the event of a potential defect in the quality of investigational supply, the sponsor may initiate a recall procedure. In this case, the investigator will be responsible for promptly addressing any request made by the sponsor to recall investigational product.

9.7. Concomitant Medications

Information on concomitant medications must be collected from the time of screening up to the 2 month visit. Following the 2 month visit through end of study participation, reporting requirements change to concomitant medications associated with reportable AEs only (vascular access related AEs and SAEs). All concomitant medications, whether prescription or non-prescription (including pharmacological doses of vitamins) with the exception of medications listed below, are to be recorded in the eCRF, using the brand name and stating dosage, indication and duration of intake.

The following medications DO NOT need to be recorded in the eCRF:

- Standard medications and IV fluids typically required for sedation, induction and maintenance of anesthesia during product implantation procedure
- Medications given during routine dialysis treatments (e.g., normal saline, hypertonic saline, etc.)

Antibiotics given, as prophylaxis for the AV fistula surgery must be recorded.

9.7.1. Prohibited Concomitant Medication

The following concomitant medications/therapies are ***prohibited***:

- Intra-surgical use of non-removable hemostats (fibrin glue, etc.)

9.8. Treatment Compliance

The Sirolimus-eluting Collagen Implant is a single-use intra-operative implant, administered by the surgical investigator. Treatment compliance is not applicable for this study.

10. ASSESSMENT OF EFFICACY

10.1. Primary Endpoint

The primary endpoint of the study is Fistula Suitability for Dialysis at 6 months (FSD6) defined as a composite of:

a. For subjects who are on hemodialysis by day 150, suitability for dialysis will be determined by the ability to use the fistula for dialysis using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min for at least two-thirds of the dialysis sessions performed during a 30 day suitability ascertainment period that will commence on day 150.
b. For subjects who are not on hemodialysis on day of enrollment and who do not initiate hemodialysis by day 150, suitability for dialysis will be determined by a vascular ultrasound performed at the 6 month follow up visit. Suitability for dialysis

will be defined as a fistula with an access vein diameter (AVD) of ≥6 mm (internal diameter) and an access blood flow of ≥500 mL/min.

Evaluation of Fistula Suitability for Dialysis at 6 months:

- For subjects undergoing hemodialysis during the suitability ascertainment period, suitability for dialysis will be based on the subject's dialysis session records
- For subjects who are not on hemodialysis on the day of enrollment (i.e. on the day of fistula creation) and who do not initiate hemodialysis by day 150, suitability for dialysis will be based on duplex ultrasound results performed at the 6 month follow up visit.

10.2. Secondary Endpoints

10.2.1. Fistula Suitability for Dialysis at 12 months

Fistula Suitability for Dialysis at 12 months (FSD12), defined as a composite of

a. For subjects who are on hemodialysis by day 330, suitability for dialysis will be determined by the ability to use the fistula for dialysis using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min for at least two-thirds of the dialysis sessions performed during a 30 day suitability ascertainment period that will commence on day 330.
b. For subjects who are not on hemodialysis on day of enrollment and who do not initiate hemodialysis by day 330, suitability for dialysis will be determined by a vascular ultrasound performed at the 12 month follow up visit. Suitability for dialysis will be defined as a fistula with an access vein diameter (AVD) of ≥6 mm (internal diameter) and an access blood flow of ≥500 mL/min.

10.2.2. Fistula Maturation by Day 90

Fistula Maturation by Day 90, defined as a composite of:

a. For subjects who are on hemodialysis by day 90:
   - Three consecutive dialysis sessions using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min, the first of these three dialysis sessions completed on or before 90 days from the time of creation of the AV fistula, or
   - Two-needle dialysis on or before 90 days with no further use of the catheter prior to achieving three consecutive dialysis sessions using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min.
b. For subjects who do not initiate hemodialysis by day 90, fistula access vein diameter (AVD) of ≥6 mm (internal diameter) and an access blood flow of ≥500 mL/min determined by a vascular ultrasound performed at the 3-month follow up visit.

Evaluation of Fistula Maturation is based on subject's dialysis session records

10.2.3. Secondary Patency

Secondary patency, defined as the interval from the time of access placement until access abandonment.

Secondary patency will be evaluated based on

- Clinical evaluation of the fistula,
- Subject's dialysis session records (for subjects who are undergoing hemodialysis),
- Imaging results (Duplex ultrasound and/or angiogram - if applicable and available), and,
- Access event data.

10.2.4. Re-intervention Rate

Re-intervention rate is defined as the total number of vascular access interventions performed during study participation to maintain or re-establish patency of the index fistula, as well as interventions to assist fistula maturation divided by the total subject participation time in the study. It is expressed as number of interventions per subject-year of exposure. Abandonment of the index fistula will count for one intervention.

If a subject's index fistula is abandoned and the subsequent subject follow-up is incomplete, that subject's participation time will be censored at the time follow-up begins to be incomplete. Each subject's follow-up time will be determined PRIOR to database lock and unblinding.

Re-intervention rates will be calculated 6 months and 12 months following fistula creation. Duration of fistula evaluation is defined as the time from fistula creation to end of study, fistula abandonment, or upon reaching a censored event.

10.3. Tertiary Endpoints

10.3.1. Time To First Dialysis (TTFD)

Time To First Dialysis (TTFD) is defined as the time from fistula creation to the time when the fistula can support three consecutive dialysis sessions using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min.

TTFD will be calculated as the time to first of three consecutive dialysis sessions meeting the above defined criteria and will be evaluated only for subjects who are on dialysis at the time of study enrollment or those who initiate dialysis on or before 28 days from the time of the AV fistula procedure.

The evaluation of TTFD will be based on the subject's dialysis session records.

10.3.2. Fistula Suitability for Dialysis at 6 months with preserved primary patency

Fistula suitability for Dialysis at 6 months with preserved primary patency, defined as a composite of

a. For subjects who are on hemodialysis by day 150, suitability for dialysis will be determined by the ability to use the fistula for dialysis using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min for at least two-thirds of the dialysis sessions performed during a 30 day suitability ascertainment period that will commence on day 150.
b. For subjects who are not on hemodialysis on day of enrollment and who do not initiate hemodialysis by day 150, suitability for dialysis will be determined by a vascular ultrasound performed at the 6 month follow up visit. Suitability for dialysis will be defined as a fistula with an access vein diameter (AVD) of ≥6 mm (internal diameter) and an access blood flow of ≥500 mL/min.

Primary Patency is defined as freedom from the first occurrence of access thrombosis or an intervention performed to maintain or re-establish access patency or assist fistula maturation.

Evaluation of Fistula Suitability for Dialysis at 6 months with preserved primary patency:

- Subject's dialysis session records (for subjects who are undergoing hemodialysis),
- 6 month duplex ultrasound results for subjects whose index fistula is not in use for hemodialysis on day 150, and,
- Access event data.

10.3.3. Fistula Suitability for Dialysis at 12 months with preserved primary patency

Fistula suitability for Dialysis at 12 months, defined as a composite of

c. For subjects who are on hemodialysis by day 330, suitability for dialysis will be determined by the ability to use the fistula for dialysis using 2-needles with a mean dialysis machine blood pump speed of ≥300 mL/min for at least two-thirds of the dialysis sessions performed during a 30 day suitability ascertainment period that will commence on day 330.
d. For subjects who are not on hemodialysis on day of enrollment and who do not initiate hemodialysis by day 330, suitability for dialysis will be determined by a vascular ultrasound performed at the 12 month follow up visit. Suitability for dialysis will be defined as a fistula with an access vein diameter (AVD) of ≥6 mm (internal diameter) and an access blood flow of ≥500 mL/min.

Primary Patency is defined as freedom from the first occurrence of access thrombosis or an intervention performed to maintain or re-establish access patency or assist fistula maturation.

Evaluation of Fistula Suitability for Dialysis at 12 months with preserved primary patency:

- Subject's dialysis session records (for subjects who are undergoing hemodialysis),
- 12 month duplex ultrasound results for subjects whose index fistula is not in use for hemodialysis on day 330, and,

- Access event data.

10.3.4. Primary Patency

Primary Patency, defined as the interval from the time of fistula creation until the first occurrence of fistula thrombosis or an intervention performed to restore/maintain patency.

The following events will NOT cause loss of primary patency:

- Intervention to ligate or occlude collateral veins,
- An invasive angiogram without an intervention (i.e., diagnostic study only),
- Procedures performed to treat steal syndrome.

Evaluation of Primary patency will be based on one or more of the following:

- Clinical evaluation of the fistula,
- Subject's dialysis session records (for subjects who are undergoing hemodialysis),
- Access event data.

10.4. Additional Definitions

10.4.1. Mean Dialysis Machine Blood Flow

Mean dialysis machine blood flow is defined as the mean of all blood flow measurements recorded after the first 30 minutes and prior to the last 30 minutes of the dialysis session. Dialysis machine blood flow (mL/min) will be obtained from the dialysis unit's electronic or paper records. Measurements made during the first 30 minutes of a dialysis session will be excluded from the determination of the mean dialysis machine blood flow since the pump speed is often increased gradually during the early portion of the dialysis session. Measurements obtained during the last 30 minutes of the dialysis session will be excluded from the determination of the session mean pump speed since the pump speed may be decreased due to fluctuations in blood pressure or in preparation for discontinuing the dialysis session.

10.4.2. Fistula Abandonment

The index AV fistula will be classified as abandoned if any of the following conditions are met:

- For subjects undergoing hemodialysis during the course of study participation:
  - The fistula was never used for 2-needle dialysis during the study period (fistula will be considered abandoned on the day of creation);
  - The fistula can no longer be used for 2-needle dialysis and there is no expectation of future use
  - Placement of a new vascular access for hemodialysis

  - The fistula undergoes surgical revision of the anastomosis.
- For subjects who were not on hemodialysis on day of enrollment and who never initiated hemodialysis during the course of study participation:
  - The fistula was designated as being abandoned by the investigator. The investigator's decision to abandon the fistula may be based on:
    - The results of a clinical evaluation of the fistula
    - In some instances, at the discretion of the investigator, the decision to abandon the fistula may be based on the results of an imaging study (ultrasound or angiogram)
  - The fistula undergoes surgical revision of the anastomosis
  - Placement of a new vascular access for hemodialysis.

10.4.3. Censored Events

Subjects experiencing censoring events before an endpoint is observed will be included in the statistical analysis up to the time at which they achieve the censoring event. They will be censored (excluded) from the analysis after that time point. These censoring rules apply to all efficacy endpoints.

Censored events include:

- Death
- Renal transplantation
- Transfer to peritoneal dialysis

11. ASSESSMENT OF SAFETY

Safety evaluations will be based on treatment emergent adverse events (TEAEs) up to the 2 month visit and vascular access events reported during the study. Treatment emergent is defined as any adverse event that emerges after the subject is enrolled (run-in and randomized) in the study. The run-in subjects' adverse events will be included in the safety evaluation. Vascular access events include access dysfunction, thrombosis, access-related hand ischemia, infiltration requiring a rest period, fistula-related bleeding, infection, problems with wound healing, aneurysm, pseudoaneurysm, and all interventional procedures performed on the study fistula. During follow-up, after the 2 month visit, the following will be reported and recorded: vascular access events, concomitant medications and therapies associated with vascular access, serious adverse events (SAEs) and AEs reported during an SAE. At each follow-up visit up to the 2 month visit, AEs and concomitant medications will be recorded. Changes in comparison to baseline and the 2 month visit that are considered to be clinically significant will be reported as AEs.

12. ADVERSE AND SERIOUS ADVERSE EVENTS

12.1. Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a subject participating in a clinical study. It includes:

- Any unfavorable and unintended sign, symptom or disease temporally associated with the use of the investigational product, whether or not considered to be caused by the investigational product
- AEs commonly observed and anticipated based on the pharmacological effect of the investigational product
- Any laboratory abnormality, vital sign, or finding from physical examination assessed as clinically significant by the investigator (note: findings from assessments and examinations done during screening are not AEs, but are recorded as medical history)
- Accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures
- Overdoses and medication errors with and without clinical consequences.

12.2. Collection and Recording of Adverse Events

12.2.1. Collection of Adverse Events

The investigator must monitor the condition of the subject throughout the study from the time of obtaining informed consent until the last visit. Findings from assessments and examinations done during screening are not AEs, but are recorded as medical history. Safety evaluations will be based on treatment emergent adverse events (TEAEs) up to the 2 month visit and vascular access events reported during the study. Vascular access events include access dysfunction, thrombosis, access-related hand ischemia, infiltration requiring a rest period, fistula-related bleeding, infection, problems with wound healing, aneurysm, pseudoaneurysm, and all interventional procedures performed on the study fistula. Treatment emergent is defined as any adverse event that emerges after the subject is enrolled (run-in and randomized) in the study. Following the 2 month visit the following will be reported and recorded: vascular access events, concomitant medications and therapies associated with vascular access, serious adverse events (SAEs) and AEs reported during an SAE.

The sources of AEs may cover:

- The subject's response to questions about his/her health (a standard non-leading question such as "How have you been feeling since your last visit?" is asked at each visit)

- Symptoms spontaneously reported by the subject
- Investigations and examinations where the findings are assessed by the investigator to be clinically significant changes or abnormalities
- Other information relating to the subject's health becoming known to the investigator (e.g., hospitalization, etc.)

12.2.2. Recording of Adverse Events

The investigator must record all AEs in the Adverse Event Log provided in each subject's eCRF from the time of enrollment up to the 2 month visit. Following the 2 month visit through end of study, reporting requirements change to only reportable AEs (vascular access events and SAEs). Information to be recorded includes:

- Adverse event
- Date of onset
- Severity
- Causal relationship to investigational product
- Action taken to investigational product
- Other action taken
- Date of outcome
- Outcome
- Seriousness

Each of the items in the Adverse Event Log is described in detail in the following sections.

Adverse Event

Adverse events must be recorded as diagnoses, if available. If not, separate signs and symptoms should be recorded. One diagnosis/symptom should be entered per record.

If a subject suffers from the same AE more than once and the subject recovers in between the events, the AEs should be recorded separately. If an AE changes in intensity, a worst-case approach should be used when recording the event, i.e., the highest intensity and the longest duration of the event.

Note the following: A procedure is not an AE; the reason for conducting the procedure is. Hospitalization is not an AE; the reason for hospitalization is. Death is not an AE, but the cause of death is (an exception is sudden death of unknown cause or any death of unknown cause, which is an SAE).

Date of Onset

The date of onset is the date when the first sign(s) or symptom(s) were first noted. If the AE is an abnormal clinically significant laboratory test or outcome of an examination, the onset date is the date the sample was taken or the examination was performed.

Severity

The following 3-point rating scale must be used for rating of the intensity of each adverse event:

- Mild: Awareness of signs or symptoms, but no disruption of usual activity
- Moderate: Event sufficient to affect usual activity (disturbing)
- Severe: Inability to work or perform usual activities (unacceptable)

Causal Relationship to Investigational Product

The following 4-point scale must be used for rating the causal relationship of the AE to the investigational product:

- **Unrelated**: Clearly and incontrovertibly due only to extraneous causes, and does not meet criteria listed under unlikely, possible or probable.
- **Unlikely**: Does not follow a reasonable temporal sequence from administration. May have been produced by the subject's clinical state, environmental factors, or other therapies administered.
- **Possible**: Follows a reasonable temporal sequence from administration. May have been produced by the subject's clinical state, environmental factors, or other therapies administered.
- **Probable**: Clear-cut temporal association with improvement on cessation of investigational product (explanted). Follows a known pattern of response to the investigational product.
- **Direct**: Clear relationship to the investigational product. Event follows a known pattern of response to the investigational product.

Adverse events with the causality assessed as unrelated or unlikely are categorized as not related to investigational product.

Adverse events with the causality assessed as possible, probable, or direct are categorized as related to investigational product and are called adverse drug reactions (ADRs).

Action Taken to Investigational Product

The action taken to the investigational product in response to an AE must be classified as one of the following:

- None
- Access Intervention
- Concomitant Medication
- Transfusion Performed
- Emergency Room Visit
- IP Explanted
- Unknown

- Other

Other Action Taken

Adverse events requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the subject. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

If medication is administered to treat the AE, this medication must be entered in the Concomitant Medication Log.

Date of Outcome

The date the subject recovered or died.

Outcome

The outcome of an AE must be classified as one of the following:

- Recovered (fully recovered or the condition has returned to the level observed at initiation of study treatment)
- Recovered with sequelae (resulted in persistent or significant disability/incapacity)
- Recovering (condition still exists and is improving)
- Not recovered (condition still exists, has not improved; condition is irreversible, recovery/resolution not possible)
- Unknown
- Fatal

12.2.3. Pregnancy and Pregnancy Outcome

Every effort must be made to avoid pregnancy during the study. If a pregnancy does occur, the sponsor must be informed within 3 calendar days, using an SAE Report Form provided by the sponsor and/or designee. Note that pregnancy itself is not an SAE. Contact details for the follow-up on the pregnancy should be provided. The mother and the fetus must be followed up at least until the birth of the infant and one month after the birth of the infant. In general, the follow-up will include the course, duration and the outcome of the pregnancy and the health of the infant. If a pregnancy results in an abnormal outcome, which the Investigator and/or sponsor consider to be related to the investigational product, this outcome will be treated as an expedited report (See Section 12.3.2.2).

12.3. Serious Adverse Events

12.3.1. Serious Adverse Event Definition

An event is defined a serious adverse event if it:	Guidance
results in death	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within four weeks after the treatment ends and irrespective of the causal relationship to the investigational product. The death of a subject enrolled in a study is per se not an event, but an outcome.
is life-threatening	The term "life-threatening" refers to an AE in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death if it were more severe.
requires in-patient hospitalization or prolongation of existing hospitalization	The term "hospitalization" means that the subject was admitted to hospital or that existing hospitalization was extended as a result of an event. Hospitalization describes a period of at least 24 hours. Over-night stay for observation, stay at emergency room or treatment on an out-patient basis do not constitute a hospitalization. However, medical judgment must always be exercised and, when in doubt, the case should be considered serious (i.e., if the case fulfills the criterion for a medically important event). Hospitalizations for administrative or social purposes do not constitute an SAE. Hospital admissions and/or surgical operations planned before study inclusion are not considered AEs, if the illness or disease existed before the subject was enrolled in the study, provided that the condition did not deteriorate during the study.
results in persistent or significant disability/incapacity	Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. If in doubt, the decision should be left to medical judgment by the investigator.
is a congenital anomaly/birth defect	Congenital anomaly/birth defect observed in any offspring of the subject conceived during treatment with the IP.
is an important medical event	Important medical events are events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include AEs that suggest a significant hazard, contraindication or precaution, occurrence of malignancy or development of drug dependency or drug abuse. Medical and scientific judgment should be exercised in deciding whether events qualify as medically important. Important medical events include any suspected transmission of an infectious agent via a medicinal product. Any organism virus or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a subject exposed to a medicinal product.

An AE caused by an overdose or medication error is considered serious if a criterion listed in the definitions above is fulfilled.

12.3.2. Collection, Recording and Reporting of Serious Adverse Events

12.3.2.1. SAE Reporting by the Investigator

The investigator and/or designee must begin reporting all Serious Adverse Events starting the day of enrollment. Events that meet the SAE criteria listed prior to enrollment, should be documented in Medical History. The investigator is responsible to review these events and ensure the subject remains eligible for participation prior to proceeding with enrollment should the event occur in the 45 day screening period. All SAEs must be reported **immediately** to the sponsor and/or designee as soon as it becomes known and not later than within 24 hours of their knowledge of the occurrence of an SAE.

The investigator and/or designee is responsible for submitting the completed SAE Report Form with the fullest possible details **within 3 calendar days** of his/her knowledge of the SAE.

Additional information relevant to the SAE such as hospital records, results from investigations, e.g., laboratory parameters, invasive procedures, scans and x-rays, and autopsy results can be uploaded in the eCRF or provided to the sponsor and/or designee using the contact details in Table 1. In any case, the investigator and/or designee, upon request from the sponsor and/or designee, must supply this information. On any copies provided, details such as subject's name, address, and hospital ID number must be concealed and instead the subject number should be provided.

The investigator and/or designee will supply the sponsor and/or designee and the IRB with any additional requested information such as results of post-mortem examinations and hospital records.

12.3.2.2. Expedited Reporting by Sponsor

The sponsor and/or designee will report all **serious adverse events and unexpected events with a reasonable possible causality to the investigational product** as judged by either the investigator or the sponsor to the relevant parties within the stipulated timelines.

SAEs will be considered reportable regardless of whether or not the investigational product was used in accordance with the provisions in the protocol, Investigator's Brochure and labeling.

12.4. Follow-up of Adverse Events and Serious Adverse Events

12.4.1. Follow-up of Adverse Events with Onset during the Study

During the study, the investigator and/or designee must follow-up on each AE until it is resolved or until the medical condition of the subject is stable.

After the subject's last visit, the investigator and/or designee must follow-up on any AE classified as serious or considered to have a reasonable possible causality to the investigational product until it is resolved or until the medical condition of the subject is stable. All such relevant follow-up information must be reported to the sponsor and/or designee. If the event is a chronic condition, the investigator and sponsor may agree that further follow-up is not required.

12.4.2. Collection of Serious Adverse Events with Onset after Last Study Visit

If an investigator and/or designee become aware of an SAE after the subject's last visit, and s/he assesses the SAE to have a reasonable possible causality to the investigational product, the case will have to be reported to the sponsor and/or designee, regardless how long after the end of the study this takes place.

12.4.3. Tissue Explant and Histology

If the study product or a segment of native vessel or any other tissue is removed for any reason during the course of the study, the explanted tissue and/or product will be sent for histopathological and microbiological analysis. In the event of an explant, the investigator and/or designee must follow expedited reporting procedures outlined in Section 12.3.2 for SAEs.

12.5. Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will:

- Evaluate safety of enrolled subjects at periodic intervals (at least every six months),
- Review the final Clinical Study Report, at the conclusion of the study.

13. STATISTICS

13.1. Statistical Analysis Plan

The content of this section is the basis for the Statistical Analysis Plan (SAP) of this study. The SAP provides full details of the analyses, data displays, and algorithms to be used for data derivations. The SAP includes the definition of major and minor protocol deviations and the link between major protocol deviations and the analysis sets. Medically trained staff will identify major and minor protocol deviations before study closure.

13.2. Determination of Sample Size

All power calculations are via EAST® 6.4. Assuming the TRUE underlying FSD6 rates are 45% for control and 76% for treatment (based on prior data), the sample size on N=200 patients contributing to the analysis has >99% power to yield a statistically significant (alpha=0.05 2-

sided) difference between treatments. Allowing for uncertainty in the prior data, if the TRUE underlying FSD6 rates are 45% and 65%, there is approximately 82% power. The minimum OBSERVED difference that would yield statistical significance is approximately 45% vs 59%.

13.3. Data Analysis Considerations

13.3.1. Analysis Sets

13.3.1.1. Full Analysis Set

The full analysis set will consist of all subjects who are randomized to treatment or control. Full details are provided in the SAP.

13.3.1.2. Safety Set

The safety set will consist of all subjects who are enrolled in the study, i.e., run-in subjects plus subjects who are randomized to treatment or control. Full details are provided in the SAP.

13.3.2. Key Endpoints

The primary endpoint is FSD6, as defined in Section 6. Each endpoint will be tested at overall alpha level of 0.05 (2-sided). Other efficacy endpoints are as mentioned in the endpoints section (Section 6).

13.3.3. Main Analysis

The null hypothesis for FSD6 is that the population proportions of subjects with FSD6 for the treatment group receiving the sirolimus eluting collagen implant [p_I, where "I" indicates implant treatment] and the control group (p_C, where "C" indicates control group) that does not receive the implant are equal. The alternative is that the proportion of subjects with FSD6 is not equal for the treatment group and the control group.

Algebraically, these hypotheses are stated as follows, where "H0" indicates the null hypothesis and "Ha" indicates the alternative hypothesis:

$$H0: p_I = p_C$$

$$Ha: p_I \neq p_C$$

"I" indicates implant treatment, and "C" indicates control treatment.

For the primary endpoint of FSD6, the proportions will be compared between treatment and control using a logistic regression model with factors for treatment and stratum.

13.3.4. Secondary Efficacy Endpoints

Time to event secondary endpoints will be analyzed by stratified log-rank test. Binary endpoints will be compared between treatments via the same logistic regression model as for the primary efficacy endpoints. Continuous secondary endpoints will be compared via analysis of covariance for a model including factors for treatment, strata, and baseline covariate if available, or non-parametric rank tests if normality or homogeneity assumptions appear substantially violated. Overall study-wise type 1 error control across secondary endpoints will be addressed via step-down testing. That is, the secondary endpoints will be tested one at a time in step-down order, until the first non-significant result, after which step-down testing will stop for purposes of supporting conclusions.

Individual patient listings will be provided for the primary and secondary endpoints.

13.3.5. Safety Analysis

13.3.5.1. Adverse Events

All treatment emergent adverse events (TEAEs) recorded during the study will be coded according to Medical Dictionary for Regulatory Activities and all AEs will be listed. Treatment emergent is defined as any adverse event that emerges after the subject is enrolled in the study. TEAEs will be tabulated by system organ class (SOC), and individual preferred terms within each SOC. The crude incidence rate of patients who experienced AEs coded with the same preferred term will be tabulated by treatment group. TEAEs will also be tabulated by worst experienced severity. A separate summary will present treatment-emergent AEs judged related (missing relationship is considered as related) to study treatment.

Adverse events leading to premature discontinuation from the study will be listed and summarized in a manner similar to that used for TEAEs.

SAEs will be listed and summarized in a manner similar to that used for TEAEs, separated into treatment-emergent SAEs, and SAEs occurring before successful creation of the AV fistula and after.

Reasons for death will be listed and summarized in a manner similar to that used for AEs, separated for treatment-emergent deaths.

Reasons for premature discontinuation from the study will be listed and summarized by frequency tables.

13.3.5.2. Baseline Variables and Concomitant Medications

Continuous demographic variables (e.g., age, weight) and disease characteristics (e.g., time since diagnosis, etc.) will be summarized using descriptive statistics. Qualitative demographic characteristics (e.g., sex, race) and disease characteristics will be summarized by counts and percentages. Other baseline patient characteristics (e.g., medical history) will only be listed. All medications will be coded according to the WHO drug code and the drug-class code. They will

be summarized for each treatment group, the number and percentages of subjects having received each medication.

13.3.6. Exploratory Analyses

Exploratory data-driven analyses can be performed with the caveat that any statistical inference will be of supportive nature rather than confirmatory.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of the sponsor and/or designee will evaluate the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the sponsor and/or designee. This will be documented in a Clinical Study Agreement between the sponsor and the investigator.

During the study, a monitor from the sponsor and/or designee will have regular contact with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, ICH-GCP, applicable SOPs, and regulatory requirements that data are being accurately recorded in the eCRF, and that investigational product accountability checks are being performed
- The Investigator will permit the monitor timely access to all data needed to perform source data verification. This includes a comparison of the data in the eCRF with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts) and dialysis runsheets.
- Record and report all protocol deviations
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the sponsor and/or designee and those SAEs that met criteria for reporting have been forwarded to the IRB

The Investigator is expected to be able to meet with the monitor during these visits. The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

14.2. Audits and Inspections

Authorized representatives of the sponsor, a regulatory authority, or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact the sponsor and/or designee immediately if contacted by a regulatory agency about an inspection.

14.3. Confidentiality of Subject Data

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). In the event that a subject revokes authorization to collect or use protected health information (PHI), the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the sponsor and/or designee may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

15.1. Protocol Amendments

Any change to this Protocol will be documented in a Protocol Amendment, issued by the sponsor, and approved by the IRB prior to its implementation.

Substantial amendments will be submitted for consideration to the approving IRBs and Regulatory Authorities, in accordance with local regulations. An approval is required for a Substantial Amendment, e.g., one which could affect the safety of the subjects, or which entails a change to the scope/design of the study, or where a new principal or coordinating investigator is included.

15.2. Deviations from the Protocol

Deviations from the protocol should not occur. If deviations occur, the investigator must inform the monitor, and the implications of the deviation must be reviewed and discussed. All deviations

must be documented (or included in eCRF data). There should be a description of the deviation, the relevant time points (visit numbers, start and stop), reason for deviation, and the corrective action taken. Deviation reports and supporting documentation must show documentation of PI review and be kept in the Investigator's File and in the Trial Master File and recorded into the eCRF.

15.3. Premature Study Termination

Both the investigator (with regard to his/her participation) and the sponsor reserve the right to terminate the study at any time. Should this become necessary, the procedures will be agreed upon after consultation between the two parties. In terminating the study, the sponsor and the investigator will ensure that adequate consideration is given to the protection of the best interests of the subjects. Regulatory authorities and IRB's will be informed.

In addition, the sponsor reserves the right to terminate the participation of individual study sites. Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter subjects at an acceptable rate.

16. ETHICS

16.1. Ethical Conduct of the Study

This study will be conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guidelines and all applicable regulations, including current United States Code of Federal Regulations (CFR), Title 21, Parts 11, 50, 54, 56, and 312 and Title 45, Part 164. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. This study will also be carried out in accordance with local legal requirements.

16.2. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB as appropriate. The investigator must submit written approval to the sponsor and/or designee before he or she can enroll any subject into the study.

The investigator and/or designee is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB upon receipt of amendments and annually, as local regulations require.

The investigator and/or designee is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The sponsor and/or designee will provide this information to the investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

16.3. Written Informed Consent

An English master version of the Subject Information and Informed Consent documents can be found in Appendix A. If the IRB and/or the study sites make changes to the Subject Information and Informed Consent documents, the amended documents must be submitted back to the sponsor and/or designee for approval.

The Investigator will obtain a freely given written consent from each subject after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the study, which are relevant to the subject's decision to participate. The study subject must be given ample time to consider participation in the study, before the consent is obtained. The subject must be able to provide consent independently; no legally authorized representatives are allowed. The Informed Consent Form must be signed and dated by the subject before he/she is exposed to any study-related procedure, including screening tests for eligibility.

The Investigator will explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify their decision.

The subject will receive a copy of his/her signed consent.

If new information becomes available that may be relevant to the study subject's willingness to continue participation in the study, an updated subject information and consent form will be forwarded to the IRB(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and re-consent will be obtained. Re-consent must be documented.

Each subject will be informed via the Informed Consent Form that the following personnel may review his/her source records and data: Monitor(s), Quality Assurance Auditor(s) mandated by the sponsor, or regulatory authority inspector(s), in accordance with applicable regulatory requirements. Data protection will be handled in compliance with national/local regulations.

17. DATA HANDLING AND RECORDKEEPING

17.1. Direct Access to Source Data/Documents

The Investigator agrees to allow the sponsor and/or designee to inspect the investigational product storage area, investigational product stocks, accountability records, subject charts and study source documents, and other records relative to study conduct. The investigator will make

the source documents for this trial available to the sponsor and/or designee, regulatory authority(ies), or health authority inspectors.

Subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by their initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the sponsor and/or designee, and the Institutional Review Board (IRB).

The information developed in this clinical study will be used by the sponsor in the clinical development of the investigational product and therefore may be disclosed by the sponsor as required for disclosure to other clinical investigators, to other pharmaceutical companies, to the FDA, to other foreign regulatory agencies and to other government agencies.

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports, made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the sponsor and shall be the sole property of the sponsor. The Investigator agrees, upon the sponsor's request and at the sponsor's expense, to execute such documents and to take such other actions, as the sponsor deems necessary or appropriate to obtain patents in the sponsor's name covering any of the foregoing.

17.2. Retention of Records

The investigator will retain all study documents for at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan), and until there are no pending or contemplated marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the investigator will retain all study documents for at least 2 years after the investigation is discontinued and regulatory authorities have been notified.

The investigator will notify the sponsor prior to destroying any study records. Should the investigator wish to assign the study records to another party or move them to another location, the sponsor and/or designee must be notified in writing in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements will be made between the investigator and the sponsor for storage. If source documents are required for continued care of the subject, appropriate copies for storage off site will be made.

18. REPORTING AND PUBLICATION

18.1. Clinical Study Report

The data and information collected during this study will be reported in a Clinical Study Report prepared by the sponsor.

18.2. Confidentiality and Ownership of Study Data

Any confidential information relating to the investigational product or the study, including any data and results from the study will be the exclusive property of the sponsor. The investigator and any other persons involved in the study will protect the confidentiality of this proprietary information belonging to the sponsor.

18.3. Publications and Public Disclosure

18.3.1. Publication Policy

At the end of the study, one or more manuscripts for joint publication may be prepared in collaboration between the Investigator(s) offered authorship and sponsor or one of its chosen affiliates. In a multi-site study based on the collaboration of many sites, any publication of results must acknowledge all sites. Results from multi-site studies must be reported in entirety in a responsible and coherent manner, and results from subsets should not be published in advance or without clear reference to the primary data. Sponsor reserves the right to be last author(s) in all publications related to this study, with a maximum of three employees of sponsor per publication. In the event of any disagreement in the content of any publication, both the investigator's and sponsor's opinion will be fairly and sufficiently represented in the publication.

Any external CRO or laboratory involved in the conduct of this study has no publication rights regarding this study.

If the Investigator wishes to independently publish/present any results from the study, the draft manuscript/presentation must be submitted in writing to sponsor for comment prior to submission. Comments will be given within four weeks from receipt of the draft manuscript. This statement does not give the sponsor any editorial rights over the content of a publication, other than to verify the accuracy of the data or to restrict the disclosure of sponsor's intellectual property. If the matter considered for publication is deemed patentable by the sponsor, scientific publication will not be allowed until after a filed patent application is published. Under such conditions the publication will be modified or delayed at the Investigator's discretion, to allow sufficient time for sponsor to seek patent protection of the invention.

18.3.2. Public Disclosure Policy

ICMJE member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical studies be registered in a public, clinical trials registry. Thus,

it is the responsibility of the sponsor to register the study in an appropriate registry, i.e., www.clinicaltrials.gov, which is sponsored by the National Institutes of Health.

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