A PHASE 3, PROSPECTIVE, RANDOMIZED, MULTICENTER, SINGLE-BLIND, CONTROLLED STUDY EVALUATING ARTERIOVENOUS FISTULA OUTCOMES WITH AND WITHOUT A PERIVASCULAR SIROLIMUS-ELUTING COLLAGEN IMPLANT (THE ACCESS 2 TRIAL)

Protocol No.:	VT-305
Investigational Product:	Sirolimus-eluting Collagen Implant
Sponsor:	Vascular Therapies, Inc. 105 Union Avenue Cresskill, NJ 07626
Date of Version:	23-Jun-2025
Version:	Version 5.1

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INVESTIGATORôS AGREEMENT

I have read Protocol VT-305 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Once the protocol has been approved by the IRB/EC, I will not modify this protocol without obtaining the prior approval of the sponsor and of the IRB/EC. I will submit any protocol modifications and/or any informed consent modifications to the sponsor and/or designee and the IRB/EC, and approval will be obtained before any modifications are implemented.

I understand the protocol and will work according to it, the principles of Good Clinical Practice (current ICH guidelines), and the Declaration of Helsinki (1964) including all amendments up to and including the Scotland revision (2000) and notes of clarification added in 2002 and 2004, local regulations, and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsorôs (and any other rele
amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

Printed Name and Signature of Principal Investigator	Date

2. SYNOPSIS

Name of Sponsor:
Vascular Therapies, Inc.

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

Name of Active Ingredient:
Sirolimus

Title of Study:
A Phase 3, Prospective, Randomized, Multicenter, Single-blind, Controlled Study evaluating Arteriovenous fistula outcomes with and without a Perivascular Sirolimus-eluting Collagen Implant (The ACCESS2 Trial)

Study center(s):
Approximately 30 centers will participate in this study.

Studied period (years):	**Phase of development:**
Estimated date first patient enrolled: 1-Sep-2022 Estimated date last patient completed: 15-Aug-2025	3

Study Objectives and Hypothesis:
The primary study objective is to evaluate the benefit of the Sirolimus-eluting Collagen implant (SeCI; Sirogen), a single dose prophylactic treatment delivered intraoperatively at the time of surgical creation of an arteriovenous fistula (index AVF) for hemodialysis vascular access (index procedure). The SeCI is intended to improve clinical maturation of the AVF, signaling readiness for initial clinical use of the vascular access. The primary study hypothesis is that in comparison to the control group, the rate of clinical fistula maturation will be higher in the treatment group.

Methodology:
This is a randomized, single-blind, multicenter study designed to evaluate the efficacy and safety of the SeCI delivered as a single intraoperative dose using the peri-adventitial route of drug delivery in End Stage Renal Disease (ESRD) subjects who are undergoing surgery for creation of a new AV fistula for hemodialysis vascular access. Subjects will be randomized 1:1 to the treatment or control group. Subjects randomized to the treatment group will receive the SeCI; subjects randomized to the control group will not receive an implant. To align with the sponsorôs study population will include only subject risk and is defined by subjects Ó65 years old, of single-stage, end to side, radiocephalic AV fistula. Randomization will be stratified by age (65-74 years ; 75Ó years), gender (at least 30% of the high risk category will be females), and region (U.S.; U.K.). The randomization scheme will be implemented via the IRT system. Enrolled subjects will be followed for a period of one year from the time of their index surgical procedure (day of randomization).

Number of patients (planned):
Planned enrollment is approximately 120 subjects randomized in equal proportions to treatment and control, stratified by age and gender.

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

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

1. Age 65 years or older
2. Able to provide written informed consent using a form that is approved by the Institutional Review Board (IRB) / Ethics Committee (EC)
3. Currently on hemodialysis for ≥ 12 months (≥ 52 months requires documented approval by the Sponsor)
4. Life expectancy of at least one year
5. In the opinion of the operating surgeon, vascular anatomy suitable for creation of a radiocephalic AV fistula
6. Successful creation of a single-stage radiocephalic 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. Prior AV access created on the limb where the fistula surgery is planned
2. Planned start of peritoneal dialysis within 6 months of randomization
3. History of steal syndrome from a previous hemodialysis vascular access requiring intervention or access abandonment
4. Known hypersensitivity to the following: sirolimus, beef or bovine collagen
5. Hypotension with systolic blood pressures <100 mm Hg at the time of screening
6. Receiving anticoagulant therapy for non-cardiac indications
7. Known bleeding disorder.
8. Known to be HIV positive
9. Prisoner, mentally incompetent, and/or current alcohol or drug abuser
10. Currently participating in another investigational study

Investigational product, dosage and mode of administration:

- Test Product: Sirolimus-eluting Collagen Implant (SeCI)
- Dose: Each drug product consists of two implants, one anastomosis (AF) and one venous (VF) implant. The anastomosis implant contains a nominal sirolimus dose of 225 mcg. The venous implant (selected by the surgeon guided by the intraoperative diameter and the length of the exposed anastomosed vein) will contain a nominal sirolimus dose of 225 mcg, 300 mcg, 337.5 mcg, or 450 mcg. Depending on the combination of the implants, the resulting nominal sirolimus dose will be 450 mcg, 525 mcg, 562.5mcg, or 675 mcg.
- Mode of Administration: Parenteral (Perivascular-Periadventitial 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 standard of care surgery for creation of an AV fistula without the SeCI or placebo collagen.

Criteria for Evaluation:

Efficacy:

The primary endpoint of the study is Clinical Fistula Maturation (FM) defined as a fistula that can be cannulated with 2-needles for at least 75% of the dialysis sessions, including 3 consecutive sessions with a mean Q_b of 300 mL/min (unless the prescribed Q_b is <300 mL/min) performed during any continuous 30 day period that commences no later than 180 days after randomization.

The primary endpoint will be summarized as a time-to-event endpoint for the SeCI and control groups by reporting the cumulative proportion of AVF that achieve FM over time [defined as the interval from randomization to the first session that the fistula can be cannulated with 2 needles (contributing to the FM definition)].

The determination that the fistula is clinically mature will be based on review of the information in the subjectôs medical records including dialys

Secondary Endpoints

1. **Fistula Suitability for Dialysis at 12 months (FSD12)** defined as a fistula that can be used for dialysis using 2-needles for at least 75% of the dialysis sessions performed during a 30 day period that commences on day 330.
2. **Secondary Patency (SP)** defined as the interval from the time of randomization until access abandonment.
3. **Time To First Dialysis (TTFD)** defined as the interval from the time of randomization to the first of three consecutive dialysis sessions using 2-needles with a mean Q_b of ≥ mL/min (unless the prescribed Q_b is <300 mL/min).
4. **Mature Fistula with Preserved Function at 12 Months (MFPF)** defined as a fistula that can be cannulated with 2 needles for at least 75% of the dialysis sessions, including 3 consecutive sessions with a mean Q_b of ≥ mL/min (unless the prescribed Q_b is <300 mL/min) performed during any continuous 30-day period that commences no later than 180 days after randomization (i.e., fistula achieves FM) AND can be used for dialysis using 2-needles for at least 75% of the for the dialysis sessions performed during a 30-day period that commences on day 330 (fistula meets requirements for FSD12).
5. **Durable Fistula Maturation (DFM)** defined as a fistula that can be cannulated with 2 needles for at least 75% of the dialysis sessions, including 3 consecutive sessions with a mean Q_b of ≥ 300 mL/min performed during any continuous 30-day period that commences no later than 180 days after randomization (i.e., fistula achieves maturation) AND can be used for dialysis using 2-needles with a mean Q_b of ≥ mL/min for the dialysis sessions performed during a 30-day period that commences on day 330.
6. **Cumulative Fistula Use (CFU)** defined as the number of dialysis sessions performed using the study fistula with 2 needles and a mean Q_b of ≥ mL/min. CFU is calculated from the time of fistula creation to the end of study period or upon reaching an intercurrent event (Fistula abandonment, Death, Transfer to PD or transplant) or is lost to follow up.
7. **Cumulative Catheter Exposure (CCE)** is defined as the number of days a hemodialysis central venous catheter (CVC) is in situ and the duration of CVC exposure is calculated from the day of fistula creation (i.e., day of randomization) to the end of study period or upon reaching an intercurrent event (Fistula abandonment, Death, Transfer to PD or transplant) or is lost to follow up.

Safety:

Safety evaluations will be based on treatment emergent vascular access adverse events reported during the study following randomization of a subject and any adverse events (AEs) that lead to premature discontinuation from the study. Treatment emergent 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, the following will be reported and recorded: vascular access events, concomitant medications and therapies associated with vascular access, AEs that lead to discontinuation, and serious adverse events (SAEs).

Data Analysis and Statistical methods

Summary statistics for demographics and important baseline parameters will be provided by treatment group and for all subjects combined.

Efficacy Analysis: The Full Analysis Set will include ALL randomized subjects. The primary endpoint, Clinical Fistula Maturation (FM), will be analyzed by stratified (by age and gender) weighted (Harrington-Fleming method) log rank test. Fistula Suitability for Dialysis at 12 months (FSD12), a binary endpoint, will be analyzed via Cochran Mantel Haenszel (CMH) test stratified by age and gender to compare proportions of patients between treatment groups.

Secondary Patency (SP) and Time to First Dialysis (TTFD), the two other time to event endpoints, will be analyzed by stratified (unweighted) log-rank test. Secondary Patency will be analyzed both as a binary endpoint and as a time-to-event endpoint. Time-to-event analysis will be the primary analysis for Secondary Patency.

A **single interim analysis** is planned when FM data are available from the first approximately 62% of the total number of evaluable patients who will be available for the planned final analysis, yielding approximately 50% for the planned number of events. For example, if the trial is initiated with the intent of enrolling 120 patients expecting to yield 96 evaluable patients after accounting for a 20% loss as a result of intercurrent events (n=24), interim analysis would be performed after FM data is available from the first 60 patients (62% of 96 =60) to yield 30 FMs (~1/2 the planned 60 events). Timing of the interim analysis will be based on speed of recruitment and evaluable patient projections of the blinded accumulating data.

The purpose of the interim analysis is to assess safety and potentially stop enrollment into the trial for an early efficacy conclusion. If enrollment is stopped early for an efficacy conclusion, all enrolled patients will be followed till completion or the 12 month end of study visit. O'Brien-Fleming type 1 error spending will be used so that for a single interim analysis at 30 FMs from approximately N=60 patients; $p<0.0046$ 1-sided is required for a statistically significant efficacy conclusion at the interim analysis. Otherwise, $p<0.0236$ 1-sided is required for a statistically significant efficacy conclusion at the final analysis to control the overall type 1 error at 0.025 1-sided. If the planned final analysis number of events changes prior to the interim analysis due to faster than expected enrolment and/or higher than expected evaluable patient rate, the type 1 error spending will be computed based on the O'Brien-Fleming type 1 error spending function and the estimated number of FMs at interim analysis and final analysis and documented prior to the interim analysis.

Similarly, if the accumulation of FMs is slower than expected to yield 60 events, the planned number of FMs for the interim and final analysis will be adjusted using the O'Brien-Fleming type 1 error spending function will be used if the interim analysis is carried out.

If the interim analysis is not conducted, then the full 0.025 1-sided type 1 error will be used for the final analysis. It is important to note that all decisions regarding timing of interim analysis and whether or not it will be carried out will be based on blinded accumulated data.

Intercurrent Events and Censoring

Subjects who have intercurrent events will be censored at the time of the intercurrent event. The intercurrent events are fistula abandonment, withdrawal from study, transfer to Peritoneal Dialysis, Renal Transplant, or Death.

Primary Estimand

Treatment: Comparison of AV Fistulae treated with SeCI and controls without the SeCI or placebo collagen (standard of care).

Target Study Population: A risk enriched clinical trial population defined by ESRD subjects ≥65y, at least 30% of whom are females, scheduled to undergo surgery for placement of a forearm RCF and in whom the FM endpoint can be evaluated; that is, all non-censored ESRD subjects.

Endpoint of Interest (Variable): The primary endpoint of the study is Clinical Fistula Maturation (FM) defined as a fistula that can be cannulated with 2-needles for at least 75% of the dialysis sessions, including 3 consecutive sessions with a mean Q_b of 300 mL/min (unless the prescribed Q_b is <300 mL/min), performed during any continuous 30 day period that commences no later than 180 days after randomization.

Intercurrent events (ICEs): Patients who have intercurrent events will be censored at the time of the intercurrent event.

Summary measure of Variable: Cumulative proportion achieving FM over time. AVF

Safety Analysis: TEAEs, SAEs, events leading to unblinding of treatment assignment (AEs of special interest), and AEs leading to premature discontinuation from the study will be summarized by counts and proportions by treatment for each body system organ class and by preferred term within class.

Sample Size Calculations:

In high risk ESRD patients over 65 years of age with RCF, prior randomized data from VT-304 suggest cumulative proportion of Clinical Fistula Maturation (FM) success of approximately 79% for SeCI versus 40% for control up to 180 days after surgery. However, examination of the Kaplan-Meier plot of the FM data suggest non-proportional hazards: (1) Neither group had any FMs up to ~Day 29; (2) Both groups had similar increases in FM cumulative % to ~20% at Day 60; (3) from Day 60 to 90, the SeCI group increased to ~50% and control group to 40%; (4) after Day 90, the SeCI group increased to ~79% and the control group remained at 40%. Assuming those VT-304 observed cumulative %ôs are the TRUE underlying one in each of those 4 intervals, observing 60 with a single interim analysis at 30 (Fleming-type error spending function). The t minimum OBSERVED cumulative %FM that would yield statistical significance based on 60 events would be ~20% at Day 60, ~50% at Day 90, and ~66% at Day 180 for SeCI versus ~20% at Day 60, ~45% at Days 90 and 180 for control.

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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
AE	Adverse event
APP	Advanced Practice Provider
AV	Arteriovenous
AVF	Arteriovenous Fistula
AVG	Arteriovenous Graft
CMH test	Cochran Mantel Haenzel test
CRO	Contract Research Organization
CVC	Central vein catheter
eCRF	Electronic Case Report Form
ESRD	End Stage Renal Disease
FM	Clinical Fistula Maturation
FSD12	Fistula Suitability for Dialysis at 12 Months
GCP	Good Clinical Practice
HD	Hemodialysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IP	Investigational Product
IRB	Institutional Review Board
IRT System	Interactive Response Technology System
mcg	Micrograms
NP	Nurse Practitioner
PA	Physicianôs Assistant
PD	Peritoneal dialysis
PI	Principal Investigator
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SeCI	Sirolimus-eluting Collagen Implant
SP	Secondary Patency

Abbreviation or Specialist Term	Explanation
SUSAR	Suspected Unexpected Serious Adverse Reaction
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, a lifesaving treatment for patients with End-Stage Renal Disease (ESRD), represents the most common form of renal replacement therapy. Successful hemodialysis, i.e., successful delivery of the dialysis prescription, requires repeated entry into the circulation (generally three times a week for in center dialysis); this entry is achieved through a functional portal called vascular access.

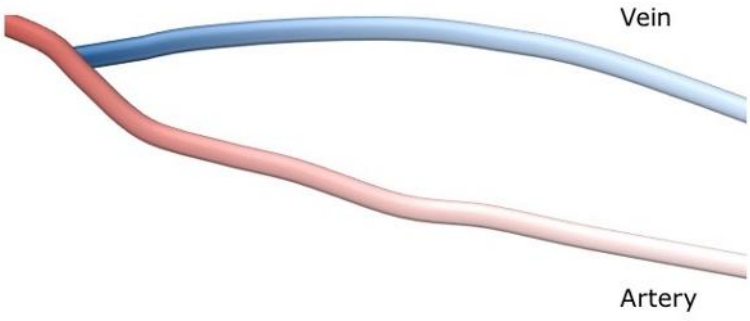
Vascular access for maintenance hemodialysis is provided via an autogenous arteriovenous fistula (AVF), a synthetic AV graft (AVG), or a prosthetic central venous catheter (CVC). The ideal vascular access would provide long-term, reliable access to the blood circulation with minimal complications. Of the three options, a *mature* arteriovenous fistula achieves this goal most successfully and is the preferred access because complication rates and health care expenditures are lower for patients with *mature, functioning fistulas* compared to those with AV grafts, as is reflected in current clinical practice guidelines (1).

5.2. Fistula Maturation and the Unmet Medical Need

5.2.1. Fistula Maturation

During surgical creation of an AV fistula, an artery and a vein are anastomosed directly to each other (Figure 1). Over the next several weeks (average 6 weeks), in response to the increased blood flow and changes in wall stress, the diameter of the vein enlarges and the wall of the vein thickens - a process referred to as fistula maturation. Fistula maturation is a complex vascular remodeling process that requires vessel dilation, marked increases in blood flow rates in the feeding artery and draining vein, and structural changes in the vessel walls (2). 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 is a prerequisite for successful suitability for dialysis.

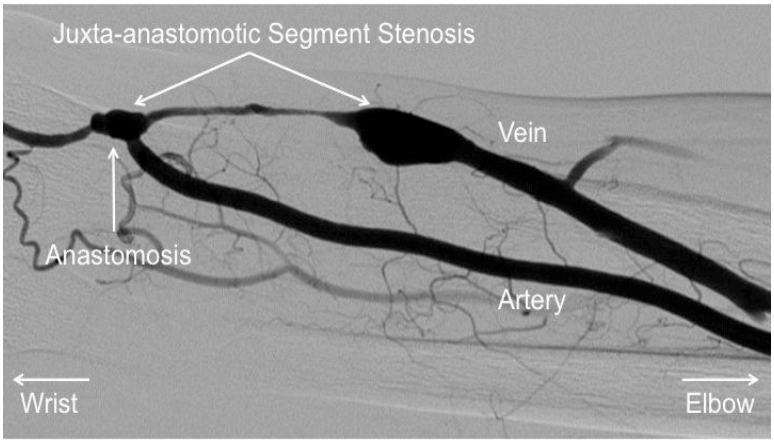
Figure 1: Arteriovenous Fistula



The problem however, is getting the fistula to mature and become functional – a mandatory outcome signaling readiness for initial clinical use thereby limiting the amount of time patients dialyze using a catheter. In contemporary practice, on average, approximately 50% of AV fistulae (Range: 35-60%) never develop to the point of being suitable for hemodialysis, and those that do, often take several months to mature (3 – 11).

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 2) (2,7,12 ï16). Roy Chaudhury and colleagues published results from analysis of histological, morphometric, and immuno-histochemical analysis of tissue samples obtained from stenotic venous segments from patients with early AV fistula failure (14). 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. Based on analysis of clinical data from a prospective randomized study, Peden et al (7) reported that a flow limiting stenosis located at and around the juxta-anastomotic segment was responsible for failure of the AVF to mature in ~ 50% of the cases.

Figure 2: Dysfunctional AV Fistula



The etiology of neointimal hyperplasia is likely multifactorial and includes trauma, vascular manipulation related to surgery, denudation of the vasa vasorum resulting in ischemic injury to the vessel wall as well as altered shear stress, i.e., exposing the low-flow, low-pressure venous conduit to high arterial pressures and flow (13,15).

5.2.2. Maturation Failure and the Unmet Medical Need

Clinically, fistula maturation failure manifests as delayed maturation or unsuccessful maturation rendering the fistula altogether unusable as a vascular access for supporting hemodialysis; the latter is not uncommon especially in the elderly patient undergoing creation of an AV fistula (4,17). Maturation failure delays initial clinical use of the fistula and prolongs catheter dependence. *A mature AVF ready for initial clinical use is a mandatory* event preceding a functional, durable AVF suitable for sustained clinical use to support hemodialysis.

Therefore, a therapeutic administered prophylactically during the time of surgical creation of the fistula that enables the fistula to mature and/or mature faster and become ready for initial clinical use is a valuable intermediate toward creating a functional, durable AVF suitable for sustained clinical use to support hemodialysis. Currently, there is no such approved prophylactic.

The lack of an approved prophylactic to address the well-recognized problem of fistula maturation failure defines the unmet medical need because in the absence of a functional fistula patients have to dialyze using a prosthetic vascular access (CVC or AVG). This deficiency is not because of a lack of effort. Over the past two decades other sponsors and organizations (NIH/NIDDK) using different drugs and biologics, some administered locally, others

systemically, have attempted to find a solution to this problem; none have succeeded (1,3,5,10,18,19). 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.

5.3. The Sirolimus-eluting Collagen Implant

The Sirolimus-eluting Collagen Implant (SeCI) is an investigational product consisting of sirolimus in an implantable, biodegradable collagen matrix. Sirolimus, the active pharmaceutical ingredient, is an approved drug, both in solution and tablet forms (Rapamune®) for the prevention of organ rejection in patients with a kidney transplant and is also the locally-eluted drug in several drug-device combination products. 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). When delivered locally to the vascular wall from a stent platform (endovascular delivery), sirolimus suppresses neointimal hyperplasia. This therapeutic effect has translated into a clinically meaningful reduction in the incidence of in-stent restenosis thereby maintaining vascular/stent patency without development of a hemodynamically significant stenosis and ischemia in the corresponding vascular bed (20 ï22).

The SeCI formulation enables sirolimus to be delivered locally to the vessel wall as a one-time parenteral dose via the perivascular-periadventitial route. Intraoperative delivery by the surgeon eliminates the variable of drug intake related to patient compliance. Furthermore, drug delivery at the time of surgical construction of the index AV Fistula eliminates need for a separate procedure for drug delivery. Local perivascular delivery of sirolimus using the 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 maintain vascular patency, a mandatory requirement for permitting the fistula to mature and become useful as a vascular access to support hemodialysis. The vascular wall action and not dependent on systemic effects. Pharmacokinetic (PK) data shows systemic release of sirolimus is negligible and there is no risk of immunosuppression.

The collagen sheet does not have any radiopaque elements or markers. Tissue collagenolytic proteases like collagenase start degrading the collagen following implantation and erode the integrity of the drug delivery matrix. The decision whether the fistula is mature and ready for initial cannulation is made on the basis of a clinical exam. The protocol does not mandate an ultrasound exam for fistula maturation assessment.

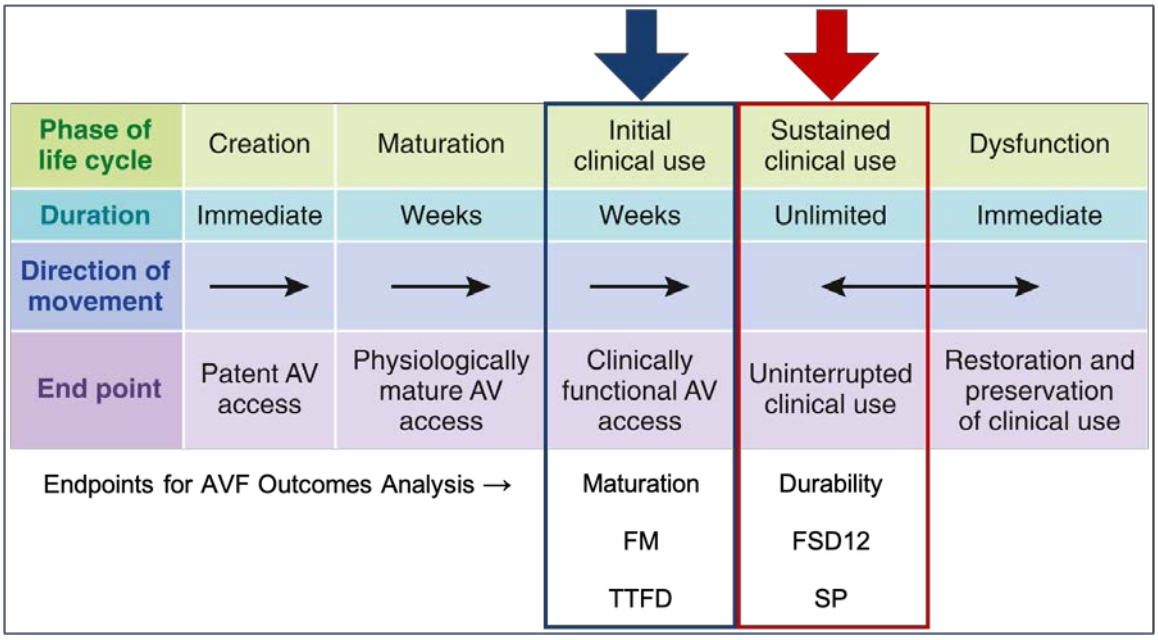
Certain features of the formulation make it uniquely suited for perivascular drug delivery. Following hydration, the implant becomes, soft, supple and easy to handle for placement around the external circumference of the target blood vessel in a cylindrical configuration. This facilitates orientation and implantation around the blood vessel. Importantly, the hydrated implant will maintain the cylindrical shape without the need for suturing the free edges, thereby avoiding the creation of a potentially restrictive external band which as a consequence can create an iatrogenic stenosis preventing the outflow vein from increasing in diameter. The matrix has adequate tensile strength to avoid tears during surgical manipulation. The biodegradability of collagen ensures that the formulation delivers the drug in a targeted manner, without a residual permanent implant that could complicate future interventions. FDA

scientists, commenting individually, have cited lack of therapeutic analysis as an essential component of FDAôs risk

5.4. Study Endpoints

A 2018 publication authored by a panel of subject matter experts convened by the Kidney Health Initiative (KHI) group emphasized the importance of a more comprehensive focus on the overall life cycle of an AV Fistula by selecting endpoints that are relevant to the type of intervention that is being studied (Figure 3). For example, for a product like the SeCI that is being developed to address fistula maturation failure, endpoints that enable evaluation of initial clinical use (a consequence of successful fistula maturation) as well as sustained clinical use of the fistula, for example at 12 months (evaluating therapeutic durability) are relevant and important. FDA is supportive of these recommendations (23).

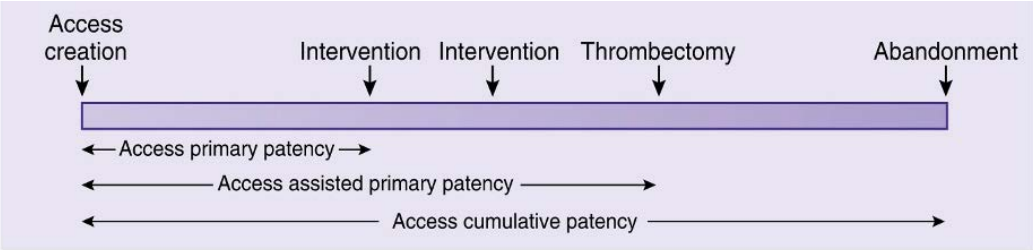
Figure 3: Corelating endpoints selected for interventional studies for AVF dialysis access with the life cycle of an AV Fistula



Adapted from Beathard et al (24)

Whereas, clinical fistula maturation (FM), the primary endpoint of the study and Time to First Dialysis (TTFD), evaluate initial clinical use of the AVF to support hemodialysis, sustained clinical use (therapeutic durability) will be evaluated using the hierarchically listed secondary endpoints of Fistula Suitability for Dialysis at 12 months (FSD12) and Secondary Patency (SP), respectively (Figure 3). The latter two endpoints provide reassurance benefit is durable and not offset by *fistula dysfunction* (evaluated by FSD12) and/or *fistula survival* (freedom from fistula abandonment evaluated by secondary/cumulative patency; Figure 4).

Figure 4: Access Patency Definitions



Adapted from Shenoy et al (25)
Secondary patency is also referred to as cumulative patency.

5.5. Catheter Use with Current Standard of Care

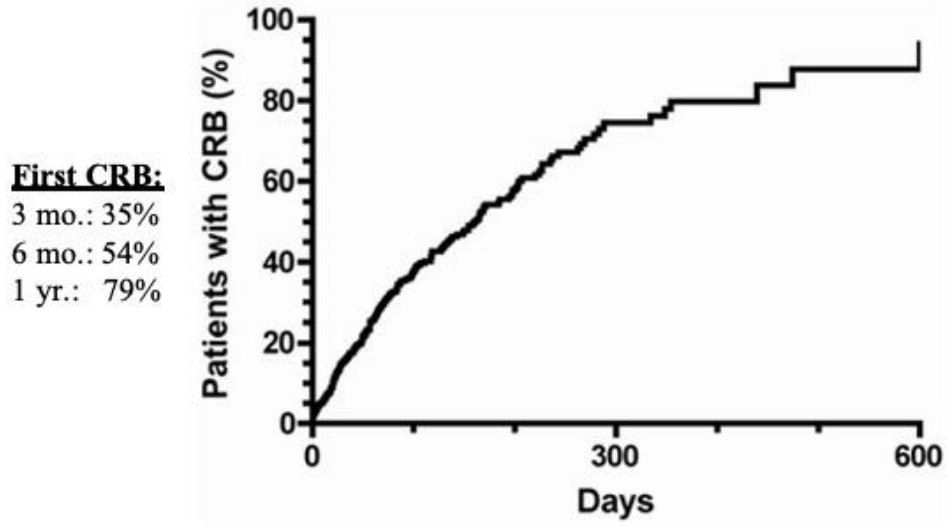
5.5.1. Catheter use in incident ESRD patients initiating Dialysis ï No change in two decades

In the United States, for the last 2 decades, at least 80% of incident ESRD patients have initiated hemodialysis using a central venous catheter and approximately 50% continue to dialyze using a catheter after 90 days (26). All these patients will continue to remain catheter dependent until an AVF (or in some cases and AVG) becomes suitable for clinical use. Achieving suitability for initial clinical use of the AVF signals freedom from catheter dependence and its associated significant adverse effects on morbidity and mortality.

The single largest vascular access related contributor to mortality and morbidity relates 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.

These time dependent CVC events (27), contribute to irreversible morbidity or mortality complications (28). Figure 5 displays the proportion of patients with catheter related bacteremia (CRB) as a function of time. By 3 months (12 weeks), 35% of the catheter dependent patients developed bacteremia; this risk progressively worsens with time.

Figure 5: Time to first catheter-related bacteremia (CRB) in patients with tunneled dialysis catheters.



Note 35% incidence of CRB by 3 months. In VT-304 the median time patients were on catheter hemodialysis before placement of an AV Fistula was 10 weeks

Bloodstream infections (BSI) are a major complication of CVC use because it increases the risk of systemic infectious complications, hospitalizations and death (29–34). Patients receiving hemodialysis spent approximately 3.5 days per patient-year hospitalized for infection, compared with 2.1 days for cardiovascular hospitalizations (35). While the adjusted rate of hospitalizations for cardiovascular causes among patients receiving hemodialysis has fallen since 2005, the hospitalization rate for infection has remained relatively stable.

5.5.2. Catheter use: Morbidity (Infections)

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. Based on data drawn from nearly all US outpatient dialysis facilities, the study by Nguyen and his colleagues from the Centers for Disease Control and Prevention (CDC) (31) concludes that rates of infection and other dialysis events when compared with other vascular access types were highest among patients dialyzed using a central venous catheter (catheter; CVC). The CDC study showed that in fact, CVC use was associated with an eight-fold increase in vascular access related blood stream infections compared to an AV fistula.

Kazakova and her colleagues from the CDC (36) reported results from a retrospective cohort study examining the incidence of hospitalization for blood stream infections (BSI) in 2,352 patients aged ≥67 years who initiated maintenance hemodialysis (HD) between January 1, 2011, and December 31, 2012. Patients were stratified according to the vascular access type at HD initiation: fistula (17.2%), central venous catheters (CVCs) have the highest risk for BSI (29.3%), followed by grafts (23.4%) and fistulas (10.1%). *The primary conclusion of the study was that in this elderly hemodialysis population, incident fistula use was associated with the lowest rates of blood stream infections.*

Patients on hemodialysis are at high risk for infection due to their immunocompromised status, with 70% of vascular access-related BSIs occurring in patients with a CVC. Between 2003 and 2013 there was an increase in the hospitalization rate for bacteremia/sepsis in both incident (38% increase) and prevalent (40% increase) ESRD patients (37). Septic emboli have the potential to cause devastating sequalae; some of these metastatic infections, for example, infective endocarditis and mycotic brain aneurysms, are life threatening with significant risk of mortality and morbidity. Given that a significant percentage of these cases are vascular access-related (29), sepsis is a potentially preventable cause of mortality in the hemodialysis population. In the 2018 USRDS report, septicemia accounted for 8% of all deaths in the ESRD population (38).

5.5.3. Catheter use: Mortality

In 2013, Ravani and colleagues reported the results of a meta-analysis of 67 cohort studies comprising 586,337 participants (32). 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)

The study by Arhuidese and colleagues [n=476,926, (39)] showed that mortality was roughly double for patients who remained on catheters compared to those who initiated dialysis with a fistula. An interesting finding in this study was although patients who started dialysis on a catheter and later switched to a fistula or graft had better survival than those who stayed on catheters, they did worse in terms of survival and infections when compared to those patients who initiated dialysis using an autogenous fistula. This study reinforces the importance of initiating dialysis with a fistula or a graft with complete freedom from catheters. These observations are particularly relevant to advanced chronic kidney disease (CKD) patients with a pre dialysis fistula.

Analyzing survival data and correlating it to the type of access used by a dialysis patient is complicated and challenging. It is confounded by the co-morbidities inherent to this patient population which confer mortality risk independent of the type of vascular access. Brown and colleagues evaluated the extent to which survival advantage may be attributable to the type of vascular access (40). *The authors concluded that favorable patient factors likely account for about two thirds of the reduced mortality seen in those dialyzed with a fistula; about a third of the overall survival advantage, however, may be attributable to the type of vascular access.*

5.6. Summary

Dialysis patients are in urgent need of a prophylactic therapeutic that can address the problem of fistula maturation failure without compromising durability of function and/or survival of the access, thereby enabling consistent, repetitive use of the AVF. The current standard of care is unable to provide a prophylactic 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 initial clinical use and remain suitable for sustained clinical use for dialysis (access durability) continues to be high priority goals in vascular access.

The clinical significance and rationale underlying selection of key study endpoints are summarized in Table 4.

Table 4: Key Study Endpoints: Clinical significance and Rationale

Endpoint	Endpoint Evaluates	Clinical Significance	Comment
Primary Endpoint Clinical Fistula Maturation (FM)	AVF that become suitable for initial clinical use	Reduces catheter dependence	Indicating readiness for cannulation to support hemodialysis is a critical event in the life cycle of the AVF and signals end of catheter dependence. Catheter use for hemodialysis increases mortality and morbidity
Secondary Endpoints Fistula Suitability for Dialysis at 12 months (FSD12) Secondary Patency (SP)	AVF that remain suitable for sustained clinical use	Demonstrates therapeutic durability	Provides reassurance that the maturation benefit is not offset by late effects that adversely impact fistula function (FSD12) and/or fistula survival (Secondary Patency).

6. STUDY ENDPOINTS AND OBJECTIVE

The primary study objective is to evaluate the benefit of the Sirolimus-eluting Collagen implant (SeCI; Sirogen), a single dose prophylactic treatment delivered intraoperatively at the time of surgical creation of an arteriovenous fistula (index AVF) for hemodialysis vascular access (index procedure). The SeCI is intended to improve clinical maturation of the AVF signaling readiness for initial clinical use of the vascular access.

The primary study hypothesis is that in comparison to the control group, the rate of clinical fistula maturation will be higher in the treatment group.

6.1. Primary Endpoint

The primary endpoint of the study is **Clinical Fistula Maturation (FM)** defined as a fistula that can be cannulated with 2-needles for at least 75% of the dialysis sessions, including 3 consecutive sessions with a mean Q_b of 300 mL/min (unless the prescribed Q_b is <300 mL/min) performed during any continuous 30 day period that commences no later than 180 days after randomization.

The primary endpoint will be summarized as a time-to-event endpoint for the SeCI and control groups by reporting the cumulative proportion of AVF that achieve FM over time [defined as the interval from randomization to the first session that the fistula can be cannulated with 2 needles (contributing to the FM definition)].

6.2. Secondary Endpoints

The secondary endpoints of the study are:

1. **Fistula Suitability for Dialysis at 12 months (FSD12)** defined as fistula that can be used for dialysis using 2-needles for at least 75% of the dialysis sessions performed during a 30 day period that will commence on day 330.
2. **Secondary Patency (SP)** defined as the interval from the time of randomization until access abandonment.
3. **Time To First Dialysis (TTFD)** defined as the interval from the time of randomization to the first of three consecutive dialysis sessions using 2-needles with a mean Q_b of Ó 3 0 0 mL/min (unless the prescribed Q_b is <300 mL/min).
4. **Mature Fistula with Preserved Function at 12 Months (MFPF)** defined as a fistula that can be cannulated with 2 needles for at least 75% of the dialysis sessions, including 3 consecutive sessions with a mean Q_b of Ó 3 0 0 mL/min (unless the prescribed Q_b is <300 mL/min) performed during any continuous 30-day period that commences no later than 180 days after randomization (i.e., fistula achieves FM) AND can be used for dialysis using 2-needles for at least 75% of the for the dialysis sessions performed during a 30-day period that commences on day 330 (fistula meets requirements for FSD12).
5. **Durable Fistula Maturation (DFM)** defined as a fistula that can be cannulated with 2 needles for at least 75% of the dialysis sessions, including 3 consecutive sessions with a mean Q_b of Ó 3 0 0 mL/min performed during any continuous 30-day period that commences no later than 180 days after randomization (i.e., fistula achieves maturation) AND can be used for dialysis using 2-needles with a mean Q_b of Ó 3 0 0 mL/min for the dialysis sessions performed during a 30-day period that commences on day 330.
6. **Cumulative Fistula Use (CFU)** defined as the number of dialysis sessions performed using the study fistula with 2 needles and a mean Q_b of Ó 3 0 0 mL/min. CFU is calculated from the time of fistula creation to the end of study period or upon reaching an intercurrent event (Fistula abandonment, Death, Transfer to PD or transplant) or is lost to follow up.
7. **Cumulative Catheter Exposure (CCE)** is defined as the number of days a hemodialysis central venous catheter (CVC) is in situ and the duration of CVC exposure is calculated from the day of fistula creation (i.e., day of randomization) to the end of study period or upon reaching an intercurrent event (Fistula abandonment, Death, Transfer to PD or transplant) or is lost to follow up.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 3, multicenter, randomized, single-blind, controlled, risk-enriched study designed to evaluate the efficacy and safety of the use of the Sirolimus-eluting Collagen Implant (SeCI) in subjects who are on 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 65 years of age, undergoing hemodialysis, and require a new single-stage radiocephalic end-to-side fistula will be eligible to participate in this study. It is expected that all subjects will be enrolled across approximately 30 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 120 subjects. Subjects will be randomized in a 1:1 ratio to yield approximately 96 evaluable subjects. To align with the sponsorôs intent of prognostic risk enrichmen who are at high risk for fistula maturation f defined by subjects Ó65 years of age, of either gender, undergoing creation of a single-stage, e end-to-side, radiocephalic AV fistula. Randomization will be stratified by age (65-74 years and Ó75 years), gender (at least 30% will be females) and region (U.S.; U.K.). The randomization scheme will be implemented via the IRT system.

Cannulation of the study fistula is not permitted prior to 28 days following the index procedure. The decision to proceed with first cannulation, based on clinical assessment of the fistula, will be made by an investigator who is blinded to the treatment assignment or an individual who may or may not be part of the study but who is qualified to prescribe the fistula cannulation order per standard of care (for example, the on call nephrologist rounding in the dialysis unit) provided this individual is unaware of the treatment assignment (i.e., blinded to treatment assignment).

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 surgical procedure (day of randomization).

7.2. Schedule of Events

A schedule of events/assessments is provided in Table 5.

Table 5: Schedule of Events

	Baseline	**Index Procedure (Day of Randomization)**	**2W Visit[a]**	**6W Visit**	**3M Visit[a]**	**6M Visit[a]**	**9M Visit[a]**	**End of Study Visit[a]**
	Ò 0 d	**0d**	**+14 ±3d**	**+42 ±3d**	**+90 ±7d**	**+180 ±15d**	**+270 ±15d**	**+360 +15d**
Informed consent	X							
Patient demographics	X							
Medical and medication history	X							
Index procedure[b]		X						
Randomization		X						
Clinical examination			X	X				
Clinical assessment of fistula status to document patency[c]		X	X	X	X	X	X	X
Fistula cannulation[d]								
Adverse events		X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X

[a] Data may be collected via phone, medical record review, and/or via electronic transfer in to the eCRF. Subject ô s dialysis session and medical records up to the time point should be reviewed for prescribed evaluations.

[b] Index procedure refers to the surgical creation of the study AV fistula. Randomization occurs on the day of the index procedure.

[c] ~~fistula~~ Clinical assessment of fistula status to document patency If fistula is in use for hemodialysis or has been abandoned, access assessment is not required. Fistula status may be r e c o r d e d i n t h e s u b j e c t ô s records via access assessments that are performed in the dialysis unit as part of standard of care.

[d] Cannulation of the study fistula is not permitted prior to 28 days following the index procedure. The decision to proceed with first cannulation, based on clinical assessment of the fistula, will be made by an investigator who is blinded to the treatment assignment or an individual who is qualified to prescribe the fistula cannulation order per standard of care (for example, the on call nephrologist rounding in the dialysis unit) provided this individual is unaware of the treatment assignment (i.e., blinded to treatment assignment).

7.3. Subject Visits

7.3.1. Baseline Ò 0days

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

The following data must be collected:

- Demographic data (age, gender, race, and ethnicity).
- Relevant medical and associated medication history. Information on relevant previous and concomitant illnesses, or any clinically significant signs or symptoms (and associated medication history) discovered as a result of screening procedures will be recorded as medical history. Particular emphasis should be given to etiology of renal failure and presence of co-morbidities like diabetes, hypertension, coronary artery disease, peripheral vascular disease, cerebrovascular disease, congestive heart failure, dyslipidemia, tobacco and alcohol use, allergies, and bleeding or clotting (thrombosis) history. Medical history should als access history.
- 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.
- Check of inclusion/exclusion criteria (see Section 8).

7.3.2. Index Procedure (0 day)

The following evaluations must be performed prior to enrollment:

- Confirmation of successful AV fistula creation. Successful creation is defined as a patent fistula with satisfactory hemostasis. Patency will be determined by the presence of a palpable thrill and any one of the following:
  - a satisfactory auditory signal using a handheld Doppler (bruit), 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**.
- Check of inclusion/exclusion criteria (see Section 8).
- **Randomization using the IRT System.**

The following assessments must be performed prior to discharge:

- Clinical assessment of fistula status to document patency.
- Assessment of AEs following completion of the index procedure and update of concomitant medications.

7.3.3. 2 Week Visit (+14±3 days)

The following information must be recorded either via in-person visit, telehealth contact, and clinical records review (subject ô s d i a l y s i s s e s s i o n s t o d a t e a n d

- 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.).
- Clinical assessment of fistula to document patency.
- Adverse event (AE) assessments include:
  - Vascular access related AEs and interventions (e.g., angiogram, angioplasty, percutaneous thrombectomy, surgical revision, surgical thrombectomy, declotting, administration of thrombolytics, etc.) since last visit.
  - Introduction/creation of a new, alternate access (catheter, AV fistula, or AV graft) since last visit.
- Update of concomitant medications.
- If subject switches renal replacement therapy modality to peritoneal dialysis (PD), collect reason for switch to PD.

7.3.4. 6 Week Visit (+42±3 days)

The following information must be **recorded via in-person visit and include clinical records review** (subject ô s d i a l y s i s s e s s i o n s t o d a t e a n d m e d i c a

- 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.).
- Clinical assessment of fistula to document patency. If fistula is in use for hemodialysis or has been abandoned, documentation of patency is not required.
- Adverse event assessments. AE assessments include:
  - Vascular access related AEs and interventions (e.g., angiogram, angioplasty, percutaneous thrombectomy, surgical revision, surgical thrombectomy, declotting, administration of thrombolytics, etc.) since last visit.
  - Introduction/creation of a new, alternate access (catheter, AV fistula, or AV graft) since last visit.
- Update concomitant medications.

- If subject switches renal replacement therapy modality to PD, collect reason for switch to PD.

7.3.5. 3 Month Visit (+90±7 days)

The following information must be recorded either via in-person visit, telehealth contact, and clinical records review (subject:ôs dialysis s

- Clinical assessment of fistula to document patency. If fistula is in use for hemodialysis or has been abandoned, documentation of patency is not required.
- Adverse event assessments. AE assessments include:
  - Vascular access related AEs and interventions (e.g., angiogram, angioplasty, percutaneous thrombectomy, surgical revision, surgical thrombectomy, declotting, administration of thrombolytics, etc.) since last visit.
  - Introduction/creation of a new, alternate access (catheter, AV fistula, or AV graft) since last visit.
- Update of concomitant medications.
- If subject switched renal replacement therapy modality to PD, collect reason for switch to PD.

7.3.6. 6 Month Visit (+180±15 days)

The following information must be recorded either via in-person visit, telehealth contact, and clinical records review (subject:ôs dialysis s

- Clinical assessment of fistula to document patency. If fistula is in use for hemodialysis or has been abandoned, documentation of patency is not required.
- Adverse event assessments. AE assessments include:
  - Vascular access related AEs and interventions (e.g., angiogram, angioplasty, percutaneous thrombectomy, surgical revision, surgical thrombectomy, declotting, administration of thrombolytics, etc.) since last visit
  - Introduction/creation of a new, alternate access (catheter, AV fistula, or AV graft) since last visit.
- Update of concomitant medications.
- If subject switched renal replacement therapy modality to PD, collect reason for switch to PD.

7.3.7. 9 Month Visit (+270±15 days)

The following information must be recorded either via in-person visit, telehealth contact, and clinical records review (subject:ôs dialysis s

- Clinical assessment of fistula to document patency. If fistula is in use for hemodialysis or has been abandoned, documentation of patency is not required.

- Adverse event assessments. AE assessments include:
  - Vascular access related AEs and interventions (e.g., angiogram, angioplasty, percutaneous thrombectomy, surgical revision, surgical thrombectomy, declotting, administration of thrombolytics, etc.) since last visit.
  - Introduction/creation of a new, alternate access (catheter, AV fistula, or AV graft) since last visit.
- Update of concomitant medications.
- If subject switched renal replacement therapy modality to PD, collect reason for switch to PD.

7.3.8. End of Study Visit (+360+15 days)

The following information must be recorded either via in-person visit, telehealth contact, and clinical records review (subject:ôs dialysis s

- Clinical assessment of fistula to document patency. If fistula is in use for hemodialysis or has been abandoned, documentation of patency is not required.
- Adverse event assessments. AE assessments include:
  - Vascular access related AEs and interventions (e.g., angiogram, angioplasty, percutaneous thrombectomy, surgical revision, surgical thrombectomy, declotting, administration of thrombolytics, etc.) since last visit.
  - Introduction/creation of a new, alternate access (catheter, AV fistula, or AV graft) since last visit.
- Update of concomitant medications.
- If subject switched renal replacement therapy modality to PD, collect reason for switch to PD.

7.4. Definition of End of Trial

The end of trial is defined as the point at which all data has been entered and queries resolved.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects Ó65 years age, of either gender undergoing a planned creation of a radiocephalic 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 subjectôs eligibility prior to enrollment. Su 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 65 years or older
2. Able to provide written informed consent using a form that is approved by the Institutional Review Board (IRB) / Ethics Committee (EC)
3. Currently on hemodialysis for ≥ 12 months (>12 months requires documented approval by the Sponsor)
4. Life expectancy of at least one year
5. In the opinion of the operating surgeon, vascular anatomy suitable for creation of a radiocephalic AV fistula
6. Successful creation of a single-stage radiocephalic 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. Prior AV access created on the limb where the fistula surgery is planned
2. Planned start of peritoneal dialysis within 6 months of randomization
3. History of steal syndrome from a previous hemodialysis vascular access requiring intervention or access abandonment
4. Known hypersensitivity to the following: sirolimus, beef or bovine collagen
5. Hypotension with systolic blood pressures <100 mm Hg at the time of screening
6. Receiving anticoagulant therapy for non-cardiac indications
7. Known bleeding disorder.
8. Known to be HIV positive
9. Prisoner, mentally incompetent, and/or current alcohol or drug abuser
10. Currently participating in another investigational study

8.3. Withdrawal or Discontinuation

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 subjectôs repr physically unavailable, the site should docum 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 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.

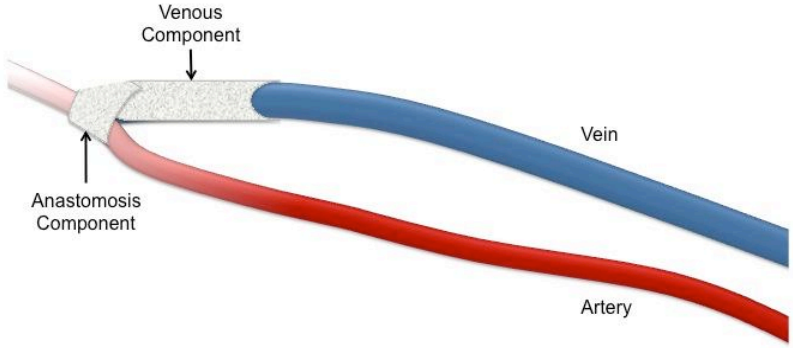
The reason for withdrawal or discontinuation will be recorded in the source document and eCRF. The investigator and/or designee will further qualify whether or not the event (leading to withdrawal, discontinuation including death, renal transplantation, or transfer to peritoneal dialysis) is related to the study treatment or not.

9. TREATMENT OF SUBJECTS

9.1. Description of Investigational Product

The Sirolimus-eluting Collagen Implant is a sterile, biocompatible, bioabsorbable, product consisting of a Type I Bovine collagen membrane combined with sirolimus. A single drug product consists of two implants; one anastomosis (AF) implant and one outflow vein (VF) implant (Figure 6). Product implantation instructions are provided in the Instructions for Use.

Figure 6: Product Implantation Scheme



The AF (anastomosis) implant spans the anastomosis and covers the peri-anastomotic segments of both vein and artery. The VF (venous) implant 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 VF implants distinguished by their unique implant codes (Table 6), appropriate for a range of blood vessel dimensions will be available. Selection of the VF implant will be an intraoperative surgical decision guided by the diameter and length of the anastomosed segment of the outflow vein.

Table 6: Description of the Component Membranes

Implant Location	Implant Code	Nominal Sirolimus Content (mcg)
Anastomosis	AF3010np	225
Outflow vein	VF1520np	225
	VF1530np	337.5
	VF2020np	300
	VF2030np	450

Depending on the size of the VF component implanted, the nominal sirolimus dose will be 450 mcg, 525 mcg, 562.5 mcg, or 675 mcg (Table 7).

Table 7: Product Matrix and Nominal Sirolimus Dosages

Implant Option	Implant Combinations	Nominal Dose (mcg)	Nominal Total Dose (mcg)
A	AF3010np + VF1520np	225 + 225	450
B	AF3010np + VF2020np	225 + 300	525
C	AF3010np + VF1530np	225 + 337.5	562.5
D	AF3010np + VF2030np	225 + 450	675

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, technique of suturing (continuous vs. interrupted), method used to occlude arterial inflow and outflow, anatomical location of the fistula (wrist or more proximally in the forearm), etc. **Hydrostatic distension of the vein and use of dilators to size or probe the vein are permitted, however, balloon dilation of the vein is not permitted**.

Following construction of the fistula once hemostasis is satisfactory, the subject will be eligible for enrollment in the study, if the outcome of the surgery is determined to be successful. Confirmation of successful AV fistula creation will be determined by the presence of a palpable thrill plus 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.

Following confirmation of successful AV fistula creation, the following measurements must be recorded:

- circumference of the exposed and mobilized outflow vein at approximately its midpoint,
- length of the outflow vein starting from the heel of the anastomosis.

9.2.2. Randomization

Following successful creation of the index AV fistula, the subject will be randomized using the IRT System.

- Randomization will be stratified by age (65-74 years and ≥ 75 years), gender (at least 30% will be females) and region (U.S.; U.K.).
- If the subject is randomized to the treatment group, the subject will receive the investigational product. The investigational product will be implanted as per instructions provided in the Instructions For Use (IFU) provided with the product. **If a topical vasodilator (e.g. Papaverine) is used during surgery, ensure that the field is irrigated and dabbed dry prior to product implantation.**
- If the subject is randomized to the control group, the surgery will be completed per standard practice, (without any implant).

Upon completion of the index procedure, the surgical incision will be closed in layers. Following completion of surgery post randomization, the completion of surgery status will be updated in the IRT System to confirm that the procedure was successfully completed.

9.2.3. Blinding/Unblinding

This study is a single-blind investigation since it will not be possible to blind the implanting surgeon, the surgical coordinator, and operating room staff, 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. Blinded personnel also include any qualified individual who is providing standard of care, is unaware of treatment assignment, and may or may not be part of the study.

An individual with knowledge of the randomization code/treatment assignment, e.g., unblinded surgeon/other unblinded individuals, will not participate and will have no role in decisions relating to fistula outcomes (e.g., fistula maturation/non-maturation, determination of fistula abandonment, need for supplementary interventions, etc.). Because of requirements/protocols specific to a local site, if a member of the surgical team needs to evaluate the AVF to declare the AVF is mature or the AVF needs a supplementary intervention, or the access needs to be abandoned, it will be done so by a surgeon or an Advanced Practice Provider (APP) like a Nurse Practitioner (NP) or Physician Assistant (PA) or other qualified individual who is blinded to the treatment assignment. This may include any qualified individual who is qualified to prescribe the fistula cannulation order per standard of care (for example, the on call nephrologist rounding in the dialysis unit) provided this individual is unaware of the treatment assignment (i.e., blinded to treatment assignment).

Any verbal or written communication that contains information that permits treatment identification is prohibited. The medical record will not contain any reference as to

whether the subject received the investigational product or not. **A statement indicating the** patientôs participation in, and Patient Initiated Study ò **VT-305 investigational study is permitted.**

In case of an emergency, if 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 via a request to the unblinded investigator and/or the Medical Monitor. The unblinded investigator and/or the Medical Monitor will authorize the blind to be broken and treatment assignment disclosed to the blinded investigator. All instances of unblinding must be reported to the study team following guidance in Section 12.5 and documented as ñadverse interest.ò

Potential sources of bias in a single blind trial and the measures to prevent information leaking from the unblinded to the blinded team are summarized in Table 8. The importance of compliance with these measures to protect the blind will be emphasized during investigator training.

Table 8: Measures to Protect the Integrity of the Blind

Potential Source of Bias	**How is this addressed?**
Unblinded personnel and Endpoint Evaluation	¶ Dialysis unit staff (blinded[a]) evaluate access at frequent intervals to determine fistula maturation (cannulation eligibility) ¶ Urgency to remove CVC is well understood by all personnel caring for the patient. There is no motivation to delay cannulat ¶ Operating surgeon and/or an individual with knowledge of the randomization code/treatment assignment will not participate in the decision to proceed with initial cannulation.
Personnel[a]	¶ Blinded staff include but are not limited to o Patient, nephrologist, Dialysis unit staff. o Because of requirements/protocols specific to a local site, if a member of the surgical team needs to evaluate the AVF to declare the AVF is mature or if the AVF needs a supplementary intervention or the access needs to be abandoned, this evaluation will be performed by a surgeon or an APP like a NP or PA who is blinded[a] to the treatment assignment. o Sponsor and/or designee who handle study monitoring, data management and analysis
Communication	¶ Any verbal or written communication enabling treatment identification is prohibited ¶ Example of permitted communication VT-305 investigational AVF studyò
Unblinding	¶ Reason for unblinding will be docu

[a] The term "Blinded personnel and/or Blinded Staff" includes any individual who is providing standard of care the subject, is unaware of treatment assignment, and may or may not be part of the study.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Packaging and Labeling

Each Sirolimus-eluting Collagen Implant (SeCI) is a sterile, single-use-only drug product and is wrapped within a Tyvek envelope, which is sealed inside a foil laminate pouch. The pouch (the primary package and sterile barrier) is packaged within a protective paperboard carton. The product is gamma sterilized and is non-pyrogenic. Each carton contains one (1) implant.

The primary package (foil pouch) is labeled with the following information: product name, implant code, drug dose, lot number, shelf life, and sponsor. The shelf carton contains this information, as well as the storage conditions, reference to the Instructions for Use, and a unique serial number. The investigational product will be labeled according to applicable guidelines and relevant regulatory agency requirements.

10.2. Storage Conditions

SeCI drug products must be stored in their original packaging in a refrigerator with controlled, restricted access at 2-8°C (36-46 F) with excursions permitted to 25°C (77°F).

10.3. 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 must be recorded as defined by the Sponsor and/or designee. Accountability 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.

10.4. Return and Destruction

Following final accountability and reconciliation, 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.

10.5. Concomitant Medications

Information on concomitant medications associated with reportable AEs only (vascular access related AEs, AEs leading to discontinuation, and SAEs) must be collected from the time of randomization up to study completion. Additionally, antibiotics given, as prophylaxis for the AV fistula surgery must be recorded in the eCRF.

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

- Immediate pre-operative and intra-operative medications administered as part of the surgical procedure (including heparin and any topical vasodilators)
- Medications given during routine dialysis treatments (e.g., normal saline, hypertonic saline, etc.)

10.5.1. Prohibited Concomitant Medication

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

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

10.6. Treatment Compliance

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

11. ASSESSMENT OF EFFICACY

11.1. Primary Endpoint

The primary endpoint of the study is **Clinical Fistula Maturation (FM)** defined as a fistula that can be cannulated with 2-needles for at least 75% of the dialysis sessions, including 3 consecutive sessions with a mean Q_b of 300 mL/min (unless the prescribed Q_b is <300 mL/min) performed during any continuous 30 day period that commences no later than 180 days after randomization.

11.2. Secondary Endpoints

11.2.1. Fistula Suitability for Dialysis at 12 months

Fistula Suitability for Dialysis at 12 months (FSD12), defined as a fistula that can be used for dialysis using 2-needles for at least 75% of the dialysis sessions performed during a 30 day period that will commence on day 330.

11.2.2. Secondary Patency

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

See Section 11.3.1 for additional definitions of fistula abandonment.

11.2.3. Time To First Dialysis

Time To First Dialysis (TTFD) defined as the interval from the time of randomization to the first of three consecutive dialysis sessions using 2-needles with a mean Q_b of ≥ 300 mL/min (unless the prescribed Q_b is <300 mL/min).

11.2.4. Mature Fistula with Preserved Function at 12 Months (MFPF)

Mature Fistula with Preserved Function at 12 Months (MFPF) defined as a fistula that can be cannulated with 2 needles for at least 75% of the dialysis sessions, including 3 consecutive sessions with a mean Q_b of ≥300 mL/min (unless the prescribed Q_b is <300 mL/min) performed during any continuous 30-day period that commences no later than 180 days after randomization (i.e., fistula achieves FM) AND can be used for dialysis using 2-needles for at least 75% of the for the dialysis sessions performed during a 30-day period that commences on day 330 (fistula meets requirements for FSD12).

11.2.5. Durable Fistula Maturation (DFM)

Durable Fistula Maturation (DFM) defined as a fistula that can be cannulated with 2 needles for at least 75% of the dialysis sessions, including 3 consecutive sessions with a mean Q_b of ≥300 mL/min performed during any continuous 30-day period that commences no later than 180 days after randomization (i.e., fistula achieves maturation) AND can be used for dialysis using 2-needles with a mean Q_b of ≥300 mL/min for the dialysis sessions performed during a 30-day period that commences on day 330.

11.2.6. Cumulative Fistula Use (CFU)

Cumulative Fistula Use (CFU) defined as the number of dialysis sessions performed using the study fistula with 2 needles and a mean Q_b of ≥300 mL/min. CFU is calculated from the time of fistula creation to the end of study period or upon reaching an intercurrent event (Fistula abandonment, Death, Transfer to PD or transplant) or is lost to follow up.

11.2.7. Cumulative Catheter Exposure (CCE)

Cumulative Catheter Exposure (CCE) is defined as the number of days a hemodialysis central venous catheter (CVC) is in situ and the duration of CVC exposure is calculated from the day of fistula creation (i.e., day of randomization) to the end of study period or upon reaching an intercurrent event (Fistula abandonment, Death, Transfer to PD or transplant) or is lost to follow up.

11.3. Additional Definitions

11.3.1. Fistula Abandonment

The following rule order will be applied in defining the occurrence and date of fistula abandonment:

- The fistula can no longer be used for 2-needle dialysis and there is no expectation of future use. The date of abandonment will be counted as the reported date of final failure/abandonment;
- Placement of a new vascular access (CVC, AVF, or AVG) or use of an existing CVC for hemodialysis because the index fistula can no longer be used for 2 needle dialysis and there is no expectation of future use. The date of abandonment will be counted as the reported date of abandonment of the index AVF or if that data is unavailable, the date when the existing CVC is used or a new access is placed;

- The fistula undergoes surgical revision of the anastomosis. The date of abandonment will be date of surgical revision of the anastomosis.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

Safety evaluations will be based on treatment emergent adverse events (TEAEs) reported during the study (following randomization of a subject). Treatment emergent adverse events are defined as any

- vascular access events including 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,
- any adverse event that leads to premature discontinuation from the study
- Serious Adverse Events

During follow-up, the following will be reported and recorded: vascular access events, adverse events leading to premature study discontinuation, serious adverse events, concomitant medications and therapies associated with vascular access, and serious adverse events (SAEs).

12.2. Adverse and Serious Adverse Events

12.2.1. Adverse Event (AE)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. Only treatment emergent vascular access events that occur after a subject has been randomized to a study arm, will be recorded.

12.2.2. Serious Adverse Event (SAE)

A serious adverse event is an AE occurring after enrollment, and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

All SAEs that occur after a subject has been randomized to a study arm, whether or not they are related to the investigational product, must be recorded.

12.3. Relationship to Study Drug

An Investigator who is qualified in medicine and is blinded to the treatment assignment must make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related or Probably Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as unrelated. If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be c

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable" the event will be co for the purposes of expedited regulatory reporting.

12.4. Recording Adverse Events

Treatment emergent adverse events revealed by observation will be recorded during the study at the investigational site. Information about AEs will be collected from the time of randomization to a study arm until the end of the study participation. Serious Adverse Event information will be collected from time of randomization to a study arm until the end of the study participation. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.2.2. An AE of severe intensity may not be considered serious.

12.5. Reporting Adverse Events

All SAEs (related and unrelated) will be recorded from the time of randomization to a study arm until the end of the study participation. All SAEs must be reported to Vascular Therapies, Inc. and/or designee within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by fax to Vascular Therapies, Inc. and/or designee.

Additional follow-up information, if required or available, should all be faxed to Vascular Therapies, Inc. and/or designee within 24 hours of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the CRF and/or study file.

All SAEs assigned by the PI and/or designee as both suspected to be related to investigational product and unexpected will be classified as SUSARs and will be subject to expedited reporting to the relevant regulatory authority(ies). Vascular Therapies, Inc. and/or designee will inform the regulatory authority(ies) of SUSARs within the required expedited reporting timeframe. Investigators will also be notified of all SUSARs that occur during the clinical trial. Each site is responsible for notifying its IRB/EC of SAEs (including any SUSARs).

13. STATISTICS

13.1. Determination of Sample Size

In high risk ESRD patients over 65 years of age with RCF, prior randomized data from VT-304 suggest Clinical Fistula Maturation (FM) success of approximately 79% for SeCI versus 40% for control. However, examination of the Kaplan-Meier plot of the FM data suggest non-proportional hazards: (1) Neither group had any FMs up to ~Day 29; (2) Both groups had similar increases in FM cumulative % to ~20% at Day 60; (3) from Day 60 to 90, the SeCI group increased to ~50% and control group to 40%; (4) after Day 90, the SeCI group increased to ~79% and the control group remained at 40%. Assuming those VT-304 observed cumul are the TRUE underlying ones at those time points, and assuming proportional hazards in each of those 4 intervals, observing 60 FMs with has ~94% single interim analysis at 30 events using O'Brien-Fleming type I error spending function). The minimum OBSERVED cumulative %FM that would yield statistical significance based on 60 events would be ~20% at Day 60, ~50% at Day 90, and ~66% at Day 180 for SeCI versus ~20% at Day 60, ~45% at Days 90 and 180 for control.

13.2. Data Analysis Considerations

13.2.1. Analysis Sets

The ITT Analysis Set comprises all randomized subjects, according to the treatment group (SeCI or control) assigned at randomization.

The Safety Analysis Set comprises all subjects who received their access placement according to the treatment actually received.

13.2.2. Intercurrent Events and Censoring

Subjects who have intercurrent events will be censored at the time of the intercurrent event. The intercurrent events are labelled and defined as follows:

- **Fistula Abandonment**. Defined as the time of the documented abandonment of the fistula for a patient.

- **Withdrawal from study**. This is defined as the time when a patient withdraws consent for participation in the study or the investigator withdraws a patient from study participation.
- **Peritoneal Dialysis**. Defined as the time when the patient initiates renal replacement therapy using peritoneal dialysis as the modality.
- **Renal Transplant**. Defined as the time when a patient undergoes renal transplant.
- **Death is also considered an intercurrent event for the analysis of fistula maturation.**

13.2.3. Sensitivity and Supplemental Analyses

Sensitivity and supplemental analyses will be carried out to assess the impact of missing data for reasons of intercurrent events other than death and renal transplant. They will be defined in the SAP.

13.2.4. Key Endpoints

The primary endpoint is FM, as defined in Section 6.1. Each endpoint will be tested at overall alpha level of 0.025 (1-sided). Other efficacy endpoints are as mentioned in the endpoints section (Section 6.2).

Primary Estimand

Treatment: Comparison of AV Fistulae treated with SeCI and controls without the SeCI or placebo collagen (standard of care).

Target Study Population: A risk enriched clinical trial population defined by ESRD subjects ≥65y, at least 30% of whom are females, scheduled to undergo surgery for placement of a forearm RCF and in whom the FM endpoint can be evaluated; that is, all non-censored ESRD subjects.

Endpoint of Interest (Variable): The primary endpoint of the study is Clinical Fistula Maturation (FM) defined as a fistula that can be cannulated with 2-needles for at least 75% of the dialysis sessions, including 3 consecutive sessions with a mean Q_b of 300 mL/min (unless the prescribed Q_b is <300 mL/min), performed during any continuous 30 day period that commences no later than 180 days after randomization.

The primary endpoint will be summarized as a time-to-event endpoint for the SeCI and control groups by reporting the cumulative proportion of AVF that achieve FM over time [defined as the interval from randomization to the first session that the fistula can be cannulated with 2-needles (contributing to the FM definition)].

Intercurrent events (ICEs): Patients who have intercurrent events will be censored at the time of the intercurrent event.

Summary measure of Variable: Cumulative proportion of AVFs that achieve FM over time

13.2.5. Main Analysis

The time to FM will be summarized by plotting the (inverted) Kaplan-Meier (KM) curves for the treatment and control groups. The KM proportions (and associated 95% CIs) for FM for the two groups will be evaluated on day 210. These estimates will be calculated stratified by age (65-74 and ≥75) and gender using the direct adjusted survival curve method (41).

The null hypothesis for testing the difference in rates of FM between control and the SeCI treatment groups is that the cumulative propo [$S_{SeCI}(t)$] is the same or lower than that for the control group [$S_c(t)$]. The alternative hypothesis is that the cumulative proportion of FMôs over t control group.

Algebraically, these hypotheses are stated as and ñHaò indicates the alternative hypothesis:

$$H0: S_{SeCI}(t) <= S_c(t)$$

$$Ha: S_{SeCI}(t) > S_c(t)$$

ñSeCIò indicates impòl ainntd itcræetaetsnecnotn, tracnld tñreatmen

The primary analysis of the primary estimand of time to FM will be based on the ITT analysis set where the cumulative rates of FM will be compared between treatment and control using the Harrington-Fleming stratified log-rank test weighted with weights p=0.25, q=0.75 (Harrington, 1982), adjusted for the stratification factors of age (65-74 and ≥75) and gender. SeCI will be consider superior to control if this statistical comparison is significant at the (one-sided) Ü = 0.025 level.

13.2.6. Interim Analysis

A single interim analysis is planned when FM data are available from the first approximately 62% of the total number of evaluable patients who will be available for the planned final analysis, yielding approximately 50% for the planned number of events. For example, if the trial is initiated with the intent of enrolling 120 patients expecting to yield 96 evaluable patients after accounting for a 20% loss as a result of intercurrent events (n=24), interim analysis would be performed after FM data is available from the first 60 patients (62% of 96 =60) to yield 30 FMs (~1/2 the planned 60 events). Timing of the interim analysis will be based on speed of recruitment and evaluable patient projections of the blinded accumulating data.

The purpose of the interim analysis is to assess safety and potentially stop enrollment into the trial for an early efficacy conclusion. If enrollment is stopped early for an efficacy conclusion, all enrolled patients will be followed till completion or the 12 month end of study visit. O'Brien-Fleming type 1 error spending will be used so that for a single interim analysis at 30 FMs from approximately N=60 patients; $p<0.0046$ 1-sided is required for a statistically significant efficacy conclusion at the interim analysis. Otherwise, $p<0.0236$ 1-sided is required for a statistically significant efficacy conclusion at the final analysis to control the overall type 1 error at 0.025 1-sided. If the planned final analysis number of events changes prior to the interim analysis due to faster than expected enrolment and/or higher than expected evaluable patient rate, the type 1 error spending will be computed based on the O'Brien-Fleming type 1 error spending function

and the estimated number of FMs at interim analysis and final analysis and documented prior to the interim analysis.

Similarly, if the accumulation of FMs is slower than expected to yield 60 events, the planned number of FMs for the interim and final analysis will be adjusted using the Lan-DeMets type 1 error spending function will be used if the interim analysis is carried out.

If the interim analysis is not conducted, then the full 0.025 1-sided type 1 error will be used for the final analysis. It is important to note that all decisions regarding timing of interim analysis and whether or not it will be carried out will be based on blinded accumulated data.

13.2.7. Secondary Efficacy Endpoints

Fistula Suitability for Dialysis at 12 months (FSD12), a binary endpoint, will be summarized by calculating the count and percentage of subjects achieving FSD12 in the SeCI treatment and control groups. The risk-difference, risk ratio, and odds ratio, with associated 95% CIs, for the difference between the two groups will be calculated. In addition, the odds ratio, adjusted for age (65-74 and ≥75) and gender, will be calculated using logistic regression. FSD12 will be analyzed as a binary endpoint using the Cochran-Mantel-Haenszel (CMH) test stratified by age (65-74 and ≥75) and gender to compare proportions of patients between SeCI and control groups.

Secondary Patency (SP) will be summarized as the cumulative proportion of abandoned AVF by plotting the (inverted SP) Kaplan-Meier (KM) curves for each treatment group and estimating the KM proportions (and associated 95% CIs) of AVF that have lost SP by day 360 or end of study visit (whichever is later). These estimates will be calculated stratified by age (65-74 and ≥75) and gender using the direct adjusted survival curve method (41). The primary analysis for Secondary Patency (SP) will be based on the ITT analysis set and will use the stratified (unweighted) log-rank test, stratifying for age (65-74 and ≥75) and gender.

TTFD will be summarized by plotting the (inverted) Kaplan-Meier (KM) curves for each group (treatment and controls) and estimating the KM proportions (and associated 95% CIs) achieving first dialysis by day 360. These estimates will be calculated stratified by age (65-74 and ≥75) and gender using the direct adjusted survival curve method (Makuch, 1982). The primary analysis for TTFD will be based on the ITT analysis set and will use the stratified (unweighted) log-rank test, stratifying for age (65-74 and ≥75) and gender.

The analyses of the secondary endpoints will be performed to assess superiority of SeCI at a 1-sided $\alpha = 0.025$ significance level. Overall type I error will be controlled using a step-down approach to testing, assessing each secondary endpoint in the following order; Fistula Suitability for Dialysis at 12 months, Secondary Patency, then Time To First Dialysis, 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.

13.2.8. Safety Analysis

13.2.8.1. Adverse Events

All adverse events recorded during the study will be coded according to Medical Dictionary for Regulatory Activities and listed. Reported AEs 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 for the Safety Analysis Set. Reported AEs will also be tabulated by worst experienced severity.

The following will be presented in separate summaries:

- Treatment-emergent AEs (TEAE) 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.
- Reasons for death will be listed and summarized in a manner similar to that used for AEs.
- Events leading to unblinding of treatment assignment (AEs of special interest) will be listed and summarized by frequency tables.

13.2.8.2. 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.

13.2.9. Exploratory Analyses

Exploratory data-driven analyses can be performed with the caveat that any statistical inference will be of supportive nature rather than confirmatory. In the event that the exploratory analyses include Primary Patency, the following events will not count as events resulting in patency loss:

- Intervention to ligate or occlude collateral veins,
- An invasive angiogram without an intervention (i.e., diagnostic study only, no intervention is required),
- Procedures performed to treat steal syndrome.
- Vein elevation procedure performed in the event there is cannulation difficulty because of the depth of the cannulation segment of the outflow vein.

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 patientôs medical records at the hospital study. This will require direct access to all original records for each patient (e.g., clinic charts and dialysis flowsheets).
- 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 local requirements of data protection and patient confidentiality. In the event that a subject revokes authorization to collect or use their health information, 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 health information, 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/EC prior to its implementation.

Substantial amendments will be submitted for consideration to the approving IRBs/ECs 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.

15.2. Deviations from the Protocol

All deviations must be documented. 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.

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 I

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 local regulations. 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/EC 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/EC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/EC 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/EC 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/EC according to local regulations and guidelines.

16.3. Written Informed Consent

An English master version of the Subject Information and Informed Consent document will be provided by the Sponsor and/or designee. If the IRB/EC 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 continue participation in the study, an updated subject information and consent form will be forwarded to the IRB(s)/EC(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 will be kept 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 this study will be given to the subjectôs personal physician or the subjectôs designated representative as appropriate. Data will 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 sponsorôs request, to assign to the sponsor any rights covering any of the foregoing, to execute such documents and to take such other actions, as the sponsor deems necessary or appropriate to obtain, perfect and enforce such rights.

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 opinion and sponsor's opinion will be fairly and

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 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 o 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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