Continued Access Study of the InterGraft™ Venous Anastomotic Connector for Minimally Invasive Connection of an Arteriovenous Graft for Hemodialysis

INVESTIGATIONAL PLAN

Clinical Trial Registration:
NCT05448950

IDE # G140221

Investigational Plan Revision History:

Rev 1, March 15, 2022: Initial release.

Sponsored by:

Phraxis, Inc.
2910 13th Terrace NW
St. Paul, MN 55112 USA
Telephone (study contact): (612) 801-6730

Reviewed and Approved by:

_____ _____
Site Principal Investigator Date

_____ _____
Sponsor representative: Date
Cindy Setum, PhD., Director of Clinical Affairs

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ACRONYMS AND ABBREVIATIONS

AE	Adverse Event
AIG	Arterial InterGraft Connector
AV	Arteriovenous
AVG	Arteriovenous graft
CEC	Clinical Events Committee
CRF	Case Report Form
DCC	Data Coordination Center
EDC	Electronic Data Capture
GCP	Good Clinical Practice
IFU	Instructions for Use
IRB	Institutional Review Board
KDOQI	Kidney Disease Outcomes Quality Initiative (National Kidney Foundation)
ePTFE	expanded Polytetrafluoroethylene
UADE	Unanticipated Adverse Device Effect
VIG	Venous InterGraft Connector
VIG-CAS	Venous InterGraft Continued Access Study

1.0 GENERAL INFORMATION

Study Name:	Continued Access Study of the InterGraft™ Venous Anastomotic Connector for Minimally Invasive Connection of an Arteriovenous Graft for Hemodialysis
Study Device:	InterGraft™ Venous Anastomotic Connector
Study Device Regulatory Status:	Investigational Device. Limited by Federal (United States) law to investigational use.
Indication for Use: (proposed)	The InterGraft™ Venous Anastomotic Connector provides a minimally invasive, sutureless method for attachment of an arteriovenous graft to a vein in the upper extremity. The InterGraft™ Venous Anastomotic Connector facilitates creation of the arteriovenous graft connection to a vein in support of hemodialysis in subjects with End Stage Renal Disease. The InterGraft™ Venous Anastomotic Connector is used together with conventional suturing of the arterial anastomosis to facilitate creation of an arteriovenous graft in support of hemodialysis in subjects with end stage renal disease.
Study Design:	Prospective, multicenter, non-randomized study
Subjects:	Up to 15 subjects with end stage renal disease who have a planned arteriovenous graft implant procedure for hemodialysis access and who meet the study selection criteria will be included.
Sponsor:	Phraxis, Inc. Saint Paul, MN Sponsor representative: Cindy Setum, Ph.D., Director of Clinical Affairs csetum@phraxis.com
Data Coordination & Statistical Analysis	Technical Resources International, Inc. Bethesda, MD Project Manager: Daniel Molina dmolina@tech-res.com
Clinical Events Committee (Chair):	Arif Asif, MD Neptune, NJ Arif.Asif@HackensackMeridian.org

2.0 INTRODUCTION AND BACKGROUND

The traditional sutured graft-to-vein anastomosis suffers from stenosis that subsequently develops due to neointimal hyperplasia. This pathology is thought to form due to surgical implant trauma to the vein and surrounding tissues, the sutures themselves, as well as turbulent flow across the anastomosis. The novel InterGraft™ Venous Anastomotic Connector (VIG) is designed to provide a minimally invasive anastomosis for arteriovenous (AVG) implantation that may avoid the pathology and clinical problems currently associated with a sutured anastomosis.

The recently completed 'VIG-only' pivotal study evaluated the safety and effectiveness of using the VIG for the venous anastomosis, together with traditional suturing of the arterial anastomosis for implantation of an AVG for hemodialysis. The VIG-only study was approved by FDA (IDE G140221) and included 158 subjects contributed from 10 USA study sites. Collected data included baseline characteristics, AVG patency and use for hemodialysis, AVG interventions, and adverse events throughout a six-month follow-up period. The primary study endpoint was cumulative graft patency at 6 months. Secondary endpoints included evaluation of primary unassisted patency at six months, the number and type of AVG interventions, and serious adverse events including rates of death, AVG infection, emergent surgery, significant bleeding and pseudoaneurysm.

Results of the VIG-only study showed that the primary endpoint of cumulative graft patency at 6 months, assessed by comparison to a target Performance Goal of 75%, was met (P-value < .001). By Kaplan Meier survival analysis, the lower 95% Confidence Bound for cumulative patency at 180 days was 86.98%. Primary unassisted patency was 60.21%, with a lower 95% Confidence Bound at 180 days of 50.84%. There were four deaths (2.5%), none of which were related to the VIG study device. Six subjects had AVG infections (3.8%) resulting in surgical excision of the graft. None of the AVG infections were related to the VIG study device. There were no reports of emergent surgery, significant bleeding or pseudoaneurysm. These results provide evidence of VIG efficacy for creating a venous anastomosis during AVG implantation, with no significant safety concerns.

Phraxis, Inc. (Sponsor) is currently preparing an application to FDA for marketing clearance of the VIG. The continued access study of the VIG (hereafter referred to as the 'Venous InterGraft Continued Access Study, or 'VIG-CAS') described in this investigational plan allows for continued enrollment of subjects while the marketing application is being prepared and subsequently review by FDA. The VIG-CAS will include the same patient population, follow-up schedule, and study endpoints as the VIG-only study.

The VIG-CAS will be conducted in compliance with the Investigational Plan, Investigational Device Exemption (IDE) regulations, Good Clinical Practice guidelines (GCP), and other applicable regulatory requirements.

3.0 STUDY DEVICE DESCRIPTION

The VIG is designed for transcatheter delivery within a 4 -7 mm diameter peripheral vein, and connection to an 6 mm AVG that has been tunneled under the skin in a standard manner. The connection is made via a small skin incision. The VIG is constructed as a nitinol framework encapsulated with ePTFE in the midsection and uncoated at the ends (**Figure 1**). The VIG distal flared end is configured as a nitinol scaffold with anchoring barbs that extend into the vein wall, and the proximal 'graft end' is a stent-like framework for anchoring within the AVG.

The VIG is intended as a permanent implant. The VIG is delivered and deployed within the target vein using a customized transcatheter delivery system. A detailed description of the VIG and delivery system is provided in the Instructions for Use (**Appendix A**).

Figure 1- InterGraft Venous Anastomotic Connector (VIG). Note barbs that anchor VIG within the vein (arrow).

Indication for Use (proposed)

The InterGraft™ Venous Anastomotic Connector provides a minimally invasive, sutureless method for attachment of an arteriovenous graft to a vein in the upper extremity. The InterGraft™ Venous Anastomotic Connector facilitates creation of the arteriovenous graft connection to a vein in support of hemodialysis in patients with End Stage Renal Disease. The InterGraft™ Venous Anastomotic Connector is intended to be used together with conventional suturing of the arterial anastomosis to facilitate creation of an arteriovenous graft in support of hemodialysis in patients with End Stage Renal Disease.

4.0 PRIOR STUDIES

The VIG, together with an arterial InterGraft Connector (AIG), were evaluated in prior studies as summarized below. The findings from the prior studies are also applicable to use of the VIG only.

NOTE: The AIG has been discontinued and it is not studied in this investigational plan.

Bench Testing

Bench testing of the VIG confirmed the structural integrity of the device, adequacy of resistance to compressive forces and radial forces, adequacy of bond strengths, kink and migration resistance, and verification of critical dimensions. Where applicable, testing was conducted using commercial 6mm ePTFE grafts that were selected due to their current widespread clinical use.

Pre-Clinical Studies

Simulated use testing was performed for verification of the VIG deployment procedure. The VIG performed adequately for intended use with respect to the ability to access, deploy and withdraw.

Acute animal studies evaluated the deliverability of the VIG, the ability to complete an AV circuit using ePTFE grafts, and near-term graft patency following initial implantation of grafts using a VIG and AIG.[1] Testing was

performed using a canine femoral artery/vein model. These studies provided evidence of safety and acceptable performance of the VIG and AIG.

Clinical Studies

First-in-Human Study

A first-in-human clinical evaluation of the VIG and AIG was performed.[2] The study was conducted at the Italian Hospital in Asuncion, Paraguay, under a protocol that was approved by the Paraguayan National Regulatory Authority and the institutional Ethics Committee. All subjects provided prior written consent, and the study was conducted in accordance with ICH Guideline for Good Clinical Practice. The InterGraft connectors were successfully used in 9/9 subjects for connection of an AVG in the upper arm: five subjects received both the VIG and the AIG, and four subjects received the VIG for the venous anastomosis and a standard sutured arterial anastomosis. Delivery and deployment success was obtained in all cases. All AVGs were patent at the end of the procedure, with no procedural adverse events related to the VIG. Three subjects exited the study early for reasons unrelated to the InterGraft connectors. The remaining subjects had patent grafts at 6 months.

VIG-only Pivotal Study (IDE G140221)

As described in **Section 2.0** above, a pivotal 'VIG-only' clinical study was conducted under an IDE approved by FDA. The study is now completed and the primary endpoint of cumulative graft patency at 6 months with comparison to a target Performance Goal of 75% was met (P-value < .001). The results of the pivotal study provide evidence of safety and effectiveness for use of the VIG and provide justification for the continued access study described in this investigational plan.

5.0 STUDY OBJECTIVE

The objective of the VIG continued access study (VIG-CAS) is to allow study investigators and their patients continued access to the VIG while a marketing application is prepared by Phraxis, Inc. and reviewed by the FDA. The study will allow for the collection of additional safety and effectiveness data using the VIG.

6.0 STUDY DESIGN

The VIG-CAS is a multicenter, prospective, single-arm (non-randomized) study that will include up to 15 subjects contributed from up to five (5) study sites/investigators who previously participated in the VIG-only study. No new investigators will be included. All subjects will be assigned to treatment with the VIG and a standard sutured arterial anastomosis for implantation of an AVG for hemodialysis. The selection criteria (patient population), follow-up schedule, and study endpoints are the same as those used in the VIG-only study.

Study data will be collected up to the point at which each subject has completed the final 6-month follow up or experienced a terminal study event.

7.0 SUBJECT SELECTION

The following inclusion and exclusion criteria must be met for enrollment in the study:

Initial Inclusion Criteria (All must be answered YES for study eligibility.)

1. Subject is ≥ 18 years of age.

2. Subject requires the creation of a vascular access graft for hemodialysis, secondary to a diagnosis of End Stage Renal Disease.

3. Subject has the vascular access graft placed in an upper extremity.

4. Baseline imaging shows suitable vascular anatomy/ vessel size for the InterGraft™ Venous Connector and an artery at least 3.5 mm in diameter that is suitable for creating the arterial anastomosis.

5. Subject has a reasonable expectation of remaining on hemodialysis for at least 6 months.

6. Subject or his/her legal guardian understands the study and is willing and able to comply with the dialysis schedule and follow-up requirements.

7. Subject or his/her legal guardian provides written informed consent. *NOTE: In accordance with the requirements of some Institutional Review Boards (IRBs), where applicable, only those subjects with capacity to consent for themselves will be included. Thus, where required by the IRB, adult individuals who lack capacity to consent for themselves will be excluded from the study.*

Final Inclusion Criterion to be applied at the time of surgery (Must be answered YES for enrollment into the study.)

8. Physician's examination at time of surgery shows no significant vessel lesions, calcification(s), anatomic structures, or abnormalities that may limit ability to safely deploy the InterGraft™ Venous Connector or create a sutured arterial anastomosis.

Exclusion Criteria (All must be answered NO for study eligibility.)

1. Subject has a documented and unsuccessfully treated ipsilateral central venous stenosis as determined by imaging.

2. Subject currently has a known or suspected bacterial, fungal, or HIV infection. *NOTE: Subjects with hepatitis B or C may be included in the study.*

3. Subject has a known hypercoagulable or bleeding disorder or requires treatment with warfarin or heparin. *NOTE: The intent of this criterion is to exclude patients with high risk for bleeding or clotting complications. Patients who are taking the oral anticoagulant Eliquis® (apixaban) may be included in the study if Eliquis is temporarily discontinued prior to the study procedure, in accordance with the approved prescribing instructions. Patients may receive anticoagulation therapy any time <u>after</u> the study AV graft implant procedure, at their physician's discretion. This should be driven by an indication unrelated to the vascular access.*

4. Subject has had a previous instance of Heparin Induced Thrombocytopenia type 2 (HIT-2) or has known sensitivity to heparin.

5. Subject has co-morbid conditions that may limit their ability to comply with study and follow-up requirements.

6. Subject has had >2 previous arteriovenous accesses in treatment arm.

7. Subject is currently taking Aggrenox®.

8. Subject needs or is scheduled for any major surgery within 30 days of the study procedure.

9. Subject is currently taking maintenance immunosuppressant medication such as rapamycin, mycophenolate or mycophenolic acid, prednisone (>10 mg), cyclosporine, tacrolimus, or cyclophosphamide.

10. Life expectancy is less than 12 months.

11. Subject is pregnant. *NOTE: A negative urine pregnancy test within 24 hours of the study procedure is required in all female subjects with reproductive capacity.*

12. Subject is a poor compliance risk (i.e.. history of IV or oral drug abuse).

13. Subject is enrolled in another dialysis or vascular investigational study.

8.0 STUDY ENDPOINTS

Study endpoints include the following:

Endpoint #1. Cumulative patency at 6 months, defined as the percentage of subjects free from loss of access of the AVG for hemodialysis, assessed at 6 months.

Endpoint #2. Acute device success, defined as AVG flow at the end of the procedure as determined by palpable graft thrill and/or audible bruit, without significant bleeding or emergent surgery.

Endpoint #3. Primary Unassisted Patency at 6 months, defined as the percentage of subjects free from the first occurrence of either access thrombosis or an access procedure performed to maintain access patency.

Endpoint #4. Time to First Cannulation, defined as the time from initial access placement to the first graft cannulation for hemodialysis.

Endpoint #5. Number and type of interventions required to maintain secondary patency.

Endpoint #6. Number and type of serious adverse events (SAEs) through 6 months. SAEs include the following: death, emergent surgery, AVG infection requiring treatment (e.g., prolonged or intravenous antibiotic therapy), significant bleeding (defined as bleeding requiring treatment), and pseudoaneurysm.

Expected interventions for restoration of patency will be documented and reported separately, are reflected in the evaluation of cumulative patency, and are not required to be reported/tabulated again as SAEs.

Endpoints will be evaluated acutely (at the time of implant), at time of any AVG intervention, at two weeks, and monthly through 6 months for all subjects. The study AVG patency evaluation will start immediately after the index procedure is completed (e.g., subject leaves the surgery suite). This means that once the AVG is created, patency evaluation begins. The occurrence of acute thrombus and treatment thereof during the index procedure while the vascular access is being created does not trigger the loss of primary patency.

9.0 SUBJECT SCREENING AND INFORMED CONSENT

Screening and Enrollment

Patients referred for AVG implant should be screened for study eligibility. A member of the Research Team will evaluate the patient for eligibility. If all initial inclusion criteria are met and no exclusion criteria are present, a member of the Research Team should inform the patient about the study's purpose and should obtain written informed consent.

Final enrollment eligibility is determined at the time of surgery, after the physician has confirmed the final inclusion criterion is met. Enrolled subjects will be assigned a unique study subject identification number. Each study site will maintain subject screening and enrollment logs. Reason for screen failures will be recorded. Screening log data will not be included in the primary database but will be reviewed during study monitoring.

Baseline Imaging

Angiographic or ultrasonic imaging of the target limb vasculature is routinely performed as part of determining the optimal AV access plan for a patient. As part of screening, baseline imaging should be reviewed to determine whether the patient meets the following criteria (as determined by the physician) for use of the VIG:

- General: Flow rate must be adequate for the creation of dialysis access, as previously mapped with ultrasound or angiography
- Vein inner diameter at planned anastomosis site is 4 -7 mm in luminal diameter
- Artery inner diameter at planned anastomosis site is at least 3.5 mm in luminal diameter

Informed Consent

A member of the Research Team will approach the subject to obtain written informed consent. The background of the study and the benefits and risks of procedures and the study should be explained to the subject. The subject (or their legal representative, if applicable) must sign the consent form prior to initiation of study procedures. The consent form used must be approved by the study site's IRB. Failure to provide consent renders the subject ineligible for the study. Subjects will be given a copy of the signed informed consent document. The signed informed consent will be retained with the study records at the site. It is the responsibility of the investigator to

assure that informed consent is obtained from each subject in accordance with the guidelines of the IRB and all applicable regulatory guidelines. A sample informed consent form is provided in **Appendix B**.

10.0 STUDY PROCEDURE

General Procedure
The procedure will be performed in accordance with the VIG Instructions for Use (IFU, **Appendix A**). A commercially available 6mm diameter ePTFE graft will be used. Conventional grafts or grafts designed for early cannulation (within 24-48 hours) may be used. The study procedure will be performed in an operating room that has fluoroscopic imaging capability for guiding placement of the VIG. The anesthesia regimen will be determined at the physician's discretion; there are no study-specific anesthesia requirements. A regional nerve block is typically performed for placement of an AVG. Standard, routine hemodynamic monitoring will be performed to assess cardiovascular status throughout the procedure. Heparin anticoagulation may be provided at the physician's discretion.

Small skin incisions will be made for tunneling the graft under the skin in a standard manner. The VIG device is provided pre-loaded within a customized catheter-based delivery system for over-the-wire delivery. The VIG is inserted through an introducer sheath placed in the target vein so that the 'vessel end' of the VIG is deployed within the vein, and the 'graft end' extends out of the vein for connection to the graft. Delivery and deployment will be performed under fluoroscopic guidance. The VIG will be deployed first, connected to the AVG, then the graft and VIG will be flushed and clamped. The arterial anastomosis will then be created using a standard suturing method.

NOTE: Although not expected, if connection of the venous graft segment using the VIG is attempted but not able to be completed, the venous anastomosis should be completed using standard suturing. Such situations will be considered as an acute device failure.

Following establishment of the AV circuit, the skin incisions will be sutured closed using standard techniques. The subject will be moved to a recovery area for monitoring prior to discharge. It is anticipated that most subjects will be discharged the same day or within 24 hours following the AVG implant procedure.

Use of Clamps
To avoid mechanical damage or disruption to the AVG or VIG, surgical clamps or other tools with teeth or other sharp features should not be used during the AVG implant procedure. An atraumatic or guarded (e.g., rubber) clamp should be used for clamping the AVG, as needed. Do not clamp or manipulate the VIG with surgical tools. Use only gentle pinching with the fingers to hold the VIG and to control hemostasis.

Additional Treatment
It is anticipated that no other interventional treatments will be required during the implant procedure. At the venous anastomotic site, no further treatment should be provided if the luminal diameter is $\geq$ 90% of the adjacent normal vessel, based on operator's assessment. If the luminal diameter is <90%, balloon angioplasty may be performed as follows:

After deployment, the nitinol-reinforced VIG may be smoothed and more fully seated against the vessel wall by inflating an angioplasty balloon. Balloon treatment should be performed according to the manufacturer's instructions, by a physician skilled in peripheral vascular interventional techniques. The balloon diameter used should be equal to that of the VIG diameter and should be no larger than 6mm when used to treat the VIG segment that is within the AVG. The balloon should be inflated within the VIG along the entire length. Multiple inflations may be needed. To avoid possible displacement of the VIG, the physician should assure that the balloon is fully deflated prior to carefully removing the balloon.

Vascular Graft for Hemodialysis

Vascular grafts that meet the following requirements, as determined by the physician, may be used: commercially available, straight (not-tapered), 6 mm inner diameter ePTFE grafts. Adequate graft length and trimming must be carefully determined to facilitate optimal positioning after the venous and arterial graft anastomoses have been completed. The graft should never be too short.

Treatment of Ipsilateral Central Venous Stenosis Prior to Enrollment

Ipsilateral central venous stenosis is a study exclusion. However, a patient with central venous stenosis may be considered for the study following successful treatment of the stenosis. Central stenosis angioplasty may be performed first, then immediately followed with the study procedure. The patient may be enrolled if, as assessed by the investigator, the central stenosis has <30% residual stenosis, which is the KDOQI threshold for successful intervention. The patient should not be enrolled if the residual stenosis is ≥ 30% or if the investigator determines that the treatment could impact the ability to assess the study endpoints (e.g., acute device success, graft patency, safety).

Study Device Failure, Defect, or Suspected Device Problem

Device malfunction is defined as *any occurrence in which the study device does not perform as intended, when used or attempted to be used in a study procedure*. As described in the IFU, a visual examination of the VIG should be performed at the time of opening the packaging and prior to use in a subject. Defective devices (obvious or suspected) should not be used. A replacement VIG should be obtained and the study procedure continued. A device accountability log will be used to account for all used and opened/unused devices in this study.

If a VIG defect or malfunction is discovered/suspected any time prior to vascular deployment, the VIG should not be used. A replacement device/component should be used and the study procedure continued. A Device Malfunction CRF must be completed for all device malfunctions, failures or suspected failures, and the defective product identification should be recorded on the device accountability log. Whenever possible, a defective/suspected defected VIG should be returned to the Sponsor for evaluation.

The Device Malfunction CRF should be used to report and provide details of situations in which the VIG does not perform as intended. Failure of the VIG to perform as intended may potentially be due to a variety of reasons, including defect or suspected defect in the device itself or the delivery system; operator error; anatomic issues; or other reasons. If use of the VIG is attempted but ultimately the device is not able to be used, a Device Malfunction CRF should be submitted to report the surrounding details.

NOTE: Device Malfunctions should be reported within 24 hours of discovery. 24-hour reporting of device malfunctions will assist with Sponsor's efforts to assess whether any SAEs associated with a device malfunction may also have occurred.

Bailout Procedure
Bailout procedures are not anticipated but could potentially be required if, for example, the VIG does not deploy correctly, does not seal correctly, is not deployed at an acceptable location, or if there are any major vascular events. In such cases, the subject should be referred for surgical intervention. No attempt should be made to remove an improperly deployed VIG using percutaneous methods.

Assessment of Graft Flow at the End of the Procedure
An AVG placed using the VIG and a sutured arterial anastomosis typically has a pulse and/or thrill which is easily palpable over the skin or directly on the AVG prior to closure of the surgical incisions. Thus, the AVG flow assessment is similar that used for standard sutured AVGs. An optimal method to confirm AVG patency at the end of the implant procedure is to feel a thrill near the arterial anastomosis or confirm a Doppler signal. Ascultation using a sterile or covered stethoscope is also acceptable. At the physician's discretion and as warranted, a final angiogram may also be performed to verify patency of the graft.

Initial Use of the Graft for Hemodialysis
Initial hemodialysis cannulation of AVGs placed with the VIG should be performed in accordance with the graft manufacturer's Instructions for Use. After needle withdrawal, use gentle, non-occlusive digital pressure to compress the cannulation site until hemostasis is achieved. The VIG should NOT be directly cannulated. In accordance with standard practice, once placed, AVGs should be used for hemodialysis access as soon as deemed appropriate by the nephrologist and/or operator. For standard ePTFE AVGs, the time from placement to first cannulation is typically after two weeks. Early cannulation AVGs can be used sooner, in accordance with approved labeling. Every effort should be made to minimize infection risk by removing central catheters as soon as possible.

11.0 FOLLOW-UP PROCEDURES AND GRAFT INTERVENTIONS

Subject Management
Prior to discharge, the study investigator or their designee should confirm that the subject understands the postoperative care requirements, as determined by the physician, and the required follow-up schedule. The two-week visit should be scheduled.

It is recommended that investigators follow the *Fistula First Guidelines* for vascular access monitoring (http://esrdnetwork18.org/pdfs/QI%20-%20FF%20Tools/FFTool_VAMPFlowChrt.pdf or current).

Pharmacologic Regimen
There are no study-specific pharmacologic requirements. The need for intraoperative and postoperative anticoagulation therapy should be based on subject history and maintained as deemed appropriate by the physician. Anticoagulation/anti-platelet therapy will be recorded on the eCRF.

Follow-up Evaluations
Subjects will be followed at two weeks and monthly thereafter through six months to assess AVG patency and any complications, if applicable. Measurement of access flow rate is part of standard care. Data from routine AV access flow monitoring performed as part of usual care, as available, will also be collected.

Graft ultrasound evaluation should be performed at the 3- and 6- month follow-up visits and the results recorded on the CRF.

NOTE: For reference and in accordance with standard care, baseline flow measurements are typically assessed during two dialysis sessions two weeks apart; and monthly measurements will be performed thereafter. An access flow rate < 500 mL/min or a drop in access flow rate of 25% from baseline should trigger an angiographic evaluation of the AVG and possible intervention.

Telephone Follow-up for Subjects Who Miss Final Visit
If a subject misses or is unavailable/unwilling to return for the final 6-month follow-up visit, telephone follow-up with the subject or their dialysis center should be attempted to determine the patency status of the AVG and to gather as much additional information as possible to complete the 6 month follow up and study completion CRFs. Telephone follow-up should be done only if the subject is unwilling or unable to return for an in-person visit. If the subject cannot be reached, then their dialysis center should be contacted (if allowed) to collect information about the most recent hemodialysis using the AVG. If it is not possible to reach the subject by phone or to contact the dialysis center, then the subject will be considered as lost-to-follow up.

Follow-up Considerations Related to the COVID-19 Pandemic
To reduce the likelihood of community exposure to COVID-19, investigators will be allowed to implement non-contact monthly study follow-up visits, in accordance with institutional and IRB requirements and approval to do so, and as deemed appropriate based on the COVID-19 pandemic situation at each site. Non-contact follow-up visits may include communications via telephone, FaceTime, email, Virtual Care or similar. In lieu of an in-person AVG patency assessment, investigators should obtain a copy of the most recent hemodialysis record as verification of AVG patency.
If non-contact follow-up is implemented due to the local pandemic situation, AVG ultrasound examinations will not be expected (at the 3- and 6-month follow-ups) and failure to perform the ultrasound examination will not be considered as a protocol deviation.

Investigators will be required to report the reason for performing non-contact follow up (due to pandemic, or other reason).

Graft Interventions
As per standard care following the AVG implant procedure, AVG interventions should be avoided within the first 7 post-operative days. As warranted and determined by the physician, standard balloon angioplasty and thrombectomy procedures may be performed within the AVG, VIG, and adjacent native artery and vein. Mechanical thrombectomy devices that use spinning, rotating or other movable parts should NOT be used within the VIG, as this may result in entanglement or other damage to the VIG. The balloon diameter used should be equal to that of the VIG diameter and should be no larger than 6mm when used to treat the VIG segment that is within the AVG.

Summary of Tests and Procedures

The required schedule for subject treatment and follow-up evaluation is shown in **Table 1**.

Table 1: Schedule of Subject Treatment and Evaluation

Timeframe (window)	Test/Procedure
Pre-procedure (within 30 days)	Baseline imaging of target AVG site (performed as part of standard care) Baseline labs: Hgb, Hct, WBC, platelets
Pre-procedure (within 24 hours)	Urine pregnancy test for female subjects with reproductive potential
Immediately following end of AVG implant procedure (before leaving surgery suite)	Confirmation of AVG flow (palpable thrill/pulse, audible bruit) At the physician's discretion and if warranted, an angiogram may also be performed to confirm patency.
Post- procedure (within 48 hours)	Post procedure labs: Hgb, Hct
At discharge	Confirmation of AVG flow (palpable thrill/pulse, audible bruit)
2 weeks following the procedure (14 +4/-7 days)	Clinical follow- up with AVG evaluation (includes collection of information regarding any subsequent hospitalization, AEs, AVG interventions)
30, 60, 90, 120, 150,180 days following the procedure (± 14 days)	Clinical follow- up with AVG evaluation (includes collection of information regarding any subsequent hospitalization, AEs, AVG interventions) AVG flow rate evaluation (ultrasound or similar) is performed at the 90-day and 180-day follow-up visits.

Final Events

The following final events will justify cessation of study follow-up: death, AVG abandonment, lost to follow up (at least 3 attempts to contact the subject should be made and documented), or completion of study follow-up.

12.0 POTENTIAL RISKS

Potential adverse events that may occur and/or require treatment with use of the VIG include but are not limited to:

- allergic reaction to device materials or procedure medications
- anastomotic disruption or tearing
- aneurysm
- artery tear or rupture
- bleeding
- bruising
- contrast dye reaction
- death
- device breakage
- dissection or 'tissue flap' in blood vessels in which the VIG has been inserted

- embolism
- hematoma
- infection
- inflammation
- kinking/compression of the AVG and/or VIG device
- migration or misplacement of VIG device
- occlusion
- pseudoaneurysm in the AVG, VIG device, or adjacent native blood vessels
- seroma
- stenosis of the AVG
- swelling of implanted arm
- thrombosis of the AVG
- vessel spasm

Many of the potential AEs listed above are similar AEs that may occur during and after AVG placement using standard surgical techniques. Potential risks of a standard surgical procedure to implant an AVG for hemodialysis include but are not limited to the following:

- failure of sutures
- bleeding immediately after the procedure
- infection
- possible need for re-operation

The VIG will be used with a standard 6 mm AVG for hemodialysis that is sold and packaged separately. Potential AEs that may occur with use of the AVG are described in the Instructions for Use packaged with the AVG.

Pregnant subjects are excluded from the study. In females of reproductive capacity, a pregnancy test must be performed prior to the procedure. This is to ensure that a fetus is not irradiated. Other potential risks to a fetus related to the study procedure are unknown.

There are no unique blood tests required for the study; however, results of standard blood tests performed to evaluate general health status at baseline, during the study procedure and during study follow-up will be included with the study data. Risks of having blood drawn include infection (rare) and bleeding (rare).

Steps to Minimize Risk
The following steps will be taken to minimize potential risks:

- The study will include only investigators who have prior training and clinical experience using the VIG.
- The study procedure will be performed in a surgical suite with radiologic imaging capabilities. If the study procedure is unable to be performed (not expected), the patient will be able to receive traditional surgical graft implantation.

13.0 POTENTIAL BENEFITS

Potential clinical benefit for the VIG is unknown. Anastomoses with the VIG may potentially reduce venous vessel trauma, improve the local vessel wall shear stresses, and promote laminar flow, thereby improving patency.

14.0 SUBJECT WITHDRAWAL FROM THE STUDY

Subjects may withdraw consent from the study at any time. Study data collected prior to withdrawal will be analyzed and included with the final study results. The investigator may withdraw the subject from the study at any time if assessed to be in the best interest of the subject.

15.0 CRITERIA FOR STUDY TERMINATION

The study may be terminated at any time for reasons of safety, based on a recommendation by the IRB, the study Clinical Events Committee (CEC), or other considerations of the Sponsor. Serious, device-related or possibly related AEs that are unexpected in either frequency or type may prompt a review by the principal investigator, CEC, and/or Sponsor, and may lead to consideration of stopping the study. Such a review and discussion will be documented and included with the study records.

16.0 STUDY DURATION

Enrollment is expected to occur over a 6-month period. Thus, completion of enrollment and 6-month follow up is anticipated within a 12-month duration.

17.0 TRAINING

Training of appropriate clinical site personnel will be the responsibility of the Sponsor or their designees. To assure uniform data collection and protocol compliance, trainers will provide an educational session to review the VIG-CAS Investigational Plan, techniques for the identification of eligible subjects, instructions on data collection, follow-up schedules and regulatory requirements. Ongoing email and telephone feedback regarding completion of eCRFs will be provided by the DCC and study monitors.

Prior to enrollment start, refresher technical training for set-up and use of the VIG will be provided. Only prior investigators with experience using the VIG will participate in the study; thus, roll-in cases will not be required.

18.0 STATISTICAL ANALYSIS

All subjects who meet the enrollment criteria and in whom use of the VIG is attempted will be included in the intention-to-treat analysis population.

Descriptive statistics will be used to summarize subject baseline and outcome data. Continuous variables will be summarized using means, standard deviations, medians, interquartile ranges, minimum and maximum values. Categorical variables will be summarized in frequency distributions. A copy of the database used to prepare clinical report summaries will be archived to enable any statistical analyses performed to be replicated. A full data listing will be prepared at the completion of the study. Listings of data represented on the CRF will include key

baseline, demographic, and outcome variables to facilitate further investigation of tabulated values and to allow for clinical review of safety variables.

No formal hypotheses will be tested or associated significance levels assigned to study results. Nominal confidence intervals may be calculated in summarizing clinical results for study endpoints but not for purposes of product labeling.

In addition to summarizing and reporting SAEs that are part of Study Endpoint #6, listings of other AEs (serious and non-serious) will be prepared and evaluated.

19.0 DATA COLLECTION AND MANAGEMENT

Data Collection
Primary data collection based on source documented medical records will be performed by study coordinators or other designated research staff at each site. A copy of the CRF (data to be collected) is provided in **Appendix C**. Electronic data capture (EDC) will be used. The EDC system used will be compliant with FDA requirements. Site training on EDC data recording will be provided by the Data Coordinating Center (DCC). All EDC training will be documented in the Investigator site file. Throughout the study, a help desk at the DCC will be available for any questions that arise from the sites concerning EDC.

Notification of subject enrollment must be provided to the Sponsor within 24 hours. The enrollment notification may be made by email to the Sponsor or by entry of an enrollment form into the EDC within 24 hours of enrollment.

The timeline for entry of CRF data into the EDC is as follows:

- Pre-procedure (baseline) Imaging, Inclusion/Exclusion, Index Procedure, and Discharge information should be entered within 7 days of enrollment.

- Follow-up Forms should be entered within 7 days of the follow-up visit.

For any deaths that may occur throughout the study duration, efforts should be made to obtain a copy of the death certificate and autopsy report, as applicable.

Data Management
The DCC will use a validated clinical data management system consisting of a relational database and a web application to capture the study data through single-pass data entry. Automated edit checks for missing, discrepant, and out of range data will be programmed into the data entry forms, and manual edits will be conducted by the DCC Managers on an ongoing basis. The Sponsor will provide a list of edit checks to the DCC.

Any data discrepancies identified during data monitoring will be communicated to study sites for resolution or justification. Once all discrepancies and queries have been resolved, the site principal investigator will confirm the data accuracy with his/her signature on a Verification CRF, or similar method. Once the study is completed,

all data have been entered into the clinical database, and all discrepancies have been resolved, an audit will be conducted to verify that all requirements for database lock have been met. The database will then be locked and final analyses performed.

CRF submission status will be tracked by the Sponsor and DCC.

20.0 DATA MONITORING AND QUALITY ASSURANCE MEASURES

Sponsor Monitoring
Study site monitoring will be performed by Sponsor personnel or Sponsor designees (contract monitors) to ensure that the study is conducted in compliance with applicable regulations and with the study protocol. A pre-investigation visit will be made to orient the staff to the study protocol and procedures, applicable regulations and requirements, and study administration expectations. Study sites will be evaluated to ensure an adequate patient base and sufficient staff support for proper study conduct.

No sites may receive shipment of study devices until the following documents are received by the sponsor:

- Written IRB approval for conduct of the study
- IRB approval of a consent form
- Signed Investigator Letter of Agreement
- Executed Study Agreement
- Copies of Investigator's CV and medical license
- Financial Disclosure

Clinical sites will be regularly monitored for timeliness and accuracy of data submitted to the DCC. Any evident patterns of noncompliance with respect to the protocol, data accuracy, maintenance of source documentation, or timeliness will be cause for the site to be put on probation. If correction actions are not made, the site will be asked to withdraw from the study.

Clinical Events Committee
An independent Clinical Events Committee (CEC) will provide medical review of SAEs, UADEs, and any deaths that may occur throughout the study. The CEC will be comprised of independent physicians with expertise in the care and management patients that comprise the potential study population. Details of CEC operations will be defined in a CEC Charter.

21.0 ADVERSE EVENTS

Definitions
Adverse Event (AE) is defined as any undesirable sign, symptom or medical or psychological condition even if the event is not considered to be related or possibly related to the study device or study procedure/intervention. Medical condition/diseases present before starting the study will be considered

adverse events only if they worsen after starting study treatment. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research. Adverse events also include any problems associated with the use of a study device that adversely affects the rights, safety or welfare of subjects.

Serious Adverse Event (SAE) is defined as any undesirable sign, symptom, or medical condition which is fatal, is life-threatening, requires or prolongs in-patient hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment. An important medical event is any AE that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

Unanticipated Adverse Event (UAE) is defined as any event or experience that meets all three criteria below:

- Is unexpected in terms of nature, severity or frequency, given the research procedures that are described in the protocol-related documents AND in the characteristics of the subject population being studied
- Related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research placed the patient or others at greater risk of harm than was previously known or recognized OR results in actual harm to the patient or others

Unanticipated Adverse Device Effects (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s).

Review and Notification of UADEs

Federal law requires that the FDA be notified immediately of all UADEs. The UADE review and notification process will be as follows:

(i) The study site will submit an Adverse Event (AE) report, indicating that the AE is serious and related or possibly related to the study device. Study sites must report all SAEs (including UADEs) to the Sponsor within 24 hours of discovery. If additional supporting information regarding the SAE is requested after the initial 24-hour report, the information will be promptly sent to the Sponsor, when available, via email.

(ii) The Sponsor will immediately conduct an evaluation and prepare a UADE report. The Sponsor will consult with the CEC as part of the UADE evaluation process.

(iii) The Sponsor will report the results of the UADE evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the Sponsor first receives notice of the UADE (§§ 812.46(b), 812.150(b)(1).

Investigator Evaluation of Adverse Events
The occurrence of AEs, including SAEs and UAEs, will be monitored throughout the study duration. Adverse event information will be collected and reported on designated AE forms and classified by the principal investigator as serious/not serious. The investigator will determine the relatedness of the AE to the study device and study procedure according to the following definitions:

- Related (AE is clearly related to the device/procedure)
- Possibly related (AE may be related to the device/procedure)
- Unrelated (AE is clearly not related to the device/procedure)

Procedure-related AEs are AEs that occur during the time interval from when the subject enters and leaves the surgical treatment suite for the index procedure (e.g., AVG implant procedure). Thus, the procedure includes use of the study device, as well as any treatments or procedures that are applied before or after the study device (eg, anesthesia, suturing of incision sites after AVG is completed), while the subject is in the surgical suite.

Device-related AEs are AEs related or possibly related to the study device or to the study device procedure which includes delivery, deployment, and attachment of the study device to the AVG.

Procedure-related events may not necessarily be related to the study device; for example, a procedure event such as an anesthesia reaction would not be related to the study device.

Device-related events may also occur after the study procedure, for example, fracture of metal strut in the VIG.

For situations in which a study subject experiences a SAE that results in abandonment of the study AV access site, the subject should be followed to the next follow-up visit after the study AVG is abandoned. This allows for collection of information about the subject's health status after the AVG is abandoned. After that visit, the subject can then be formally exited from the study. This means that the date that AVG patency is lost and the date of study withdrawal are not necessarily the same date.

Reporting and Review of Serious Adverse Events
SAEs must be reported to the Sponsor within 24 hours of discovery, and to national and local regulatory authorities, in accordance with national and local policies and procedures. In addition, all UADEs will be evaluated at the time of discovery and reported to the Sponsor within 24 hours. SAEs are reported by email or telephone call, using a designated SAE reporting form provided by the Sponsor.

A final determination as to whether an SAE meets the requirements for expedited reporting to the FDA and participating IRBs will be made by the Sponsor.

Reporting Deaths
Data regarding a subject death should be recorded on the AE/SAE CRF as follows:

If the outcome of an AE is reported as FATAL, then the STOP DATE of the AE should be date of the death. The AE with the fatal outcome will generally be the 'cause of death' as stated in source documents. The AE causing the death should be recorded on the CRF either by selecting from the checklist of specified AEs OR by selecting "Other" and then specifying the AE causing the death.

If a death is discovered during follow-up and there is no information available regarding the AE(s) leading to the death outcome, and mark as "other" for AE type. Record 'fatal' for the outcome. The START DATE and STOP DATE recorded should be the same date, eg the date of death. In the "Event Summary" section, provide the date of death. Complete as much information as possible on the CRF.

For all deaths, a copy of source document information (e.g., death record, hospital admission and discharge summary, etc) should be provided, if available. Deaths should be reported to the Sponsor within 24 hours of discovery, along with any available source documents describing the death, as available. Additional Source document information regarding the death, as may be requested by the CEC, should be provided as soon as it becomes available.

22.0 PROTOCOL VIOLATIONS

Protocol Violation is defined as any change, deviation, or departure from the study design or procedures of the research project that is not approved by the IRB and study sponsor prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), national or local regulations. Protocol violations may or may not be under the control of the research team or hospital staff.

Major Protocol Violations
All major protocol violations must be reported to the IRB, as applicable and in accordance with local IRB policy, AND to the study sponsor, immediately upon discovering them, and no later than seven (7) calendar days from the time the study team receives knowledge of the event**.**

A major violation is a protocol violation that meets the following criteria:

- Represent a serious or continuing failure on the part of the study team to comply with the protocol, standard operating procedures, GCPs, federal, state or local regulations
- Impacts subject safety or substantially alter risks to subjects. May or may not result in actual harm (clinical, emotional, social, financial, etc)
- Significantly damages the completeness, accuracy and reliability of the data collected for the study
- Is under control of the investigator/research team/hospital staff.

Any evident patterns of noncompliance with the protocol requirements will be cause for the site to be put on probation for a period of one month. If corrective actions are not made, the site will be asked to withdraw from the study.

A log of all protocol deviations should be maintained in the study regulatory binder.

23.0 REGULATORY RESPONSIBILITIES AND CONSIDERATIONS

The responsibilities described in this section are required by Federal law and regulation (21 CFR 812, Investigation Device Exemptions; 21CFR 50, Protection of Human Subjects; 21 CFR 56, Institutional Review Boards).

Investigator Responsibilities

The study site investigator is responsible for ensuring that the study is conducted according to all signed agreements, the study protocol, and applicable FDA regulations. These responsibilities are listed below. In addition, each investigator must complete and sign the Investigator's Letter of Agreement provided by the Sponsor.

- IRB approval. The investigator must submit the study protocol to his/her IRB and obtain their written approval before being allowed to participate in the study. The investigator is also responsible for fulfilling any conditions of approval imposed by the IRB.
- Informed consent. Part of the IRB approval will include approval of Informed Consent text specific to the study. The investigator must administer the approved informed consent text to each prospective study subject, and obtain the subject's signature on the text, prior to study enrollment.
- Study coordinator. To assure proper execution of the protocol, site investigators must identify a study coordinator for the site. Working under the authority of the investigator, the coordinator will assure that study requirements are fulfilled, and will be the key contact person at the site for all aspects of study administration.
- Records. Site investigators must maintain accurate, complete, and current records relating to the conduct of the study. Such records include key study related correspondence (e.g., correspondence with IRB, DCC, sponsor, study monitors); study device accountability records; subject case history information (CRFs, consent form, AE records).
- The study site principal investigator has overall responsibility for supervision of the use of the study device. The study investigator shall permit the device to be used only with subjects under his/her supervision.
- Reporting requirements. The investigator is responsible for reporting any unanticipated adverse device effects, SAEs, protocol violations, withdrawal of IRB approval, and other required reports (progress report and final report) according to the FDA guidelines and ICH GCP guidelines.

Sponsor Responsibilities

Phraxis, Inc. is the manufacturer of the VIG study device, the Sponsor of the study, and the IDE holder. The Sponsor's responsibilities include:

- Ensure that the study is conducted according to the signed study site clinical agreement, investigational plan and protocol, ICH GCP guidelines, and all applicable regulatory regulations.
- Provide study devices to participating study sites
- Provide study device training to investigators and study site staff
- Select the Principal investigator, site investigators, study sites and other study consultants (e.g. DCC) who participate in the study
- Provide financial support to study sites and consultants per individual Agreements
- Establish regulatory standards per federal regulations for clinical study sites and other study participants and perform regular site monitoring to assure compliance with them.
- Perform site monitoring of clinical data at study sites

The Sponsor (Phraxis) retains ownership of all clinical data generated in the study and controls the use of the data for purposes of regulatory submission to the US and other governments.

Supply of Study Devices

VIG devices will be provided to each study site per the terms of a Study Agreement between Phraxis, Inc. and the site. At the cessation of the study, all unused study devices will be dispositioned per the agreements between the site and Phraxis, Inc.

Record Retention Policy

Study documents should be retained for at least two years after the last approval of a marketing application, and until there are no pending or contemplated marketing applications; OR at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. The Sponsor will inform in writing when study documents are no longer needed. Study sites should not destroy any study records without first confirming with the sponsor.

24.0 MEASURES TO AVOID BIAS

Measures that will be used to avoid bias include:

- Use of independent CEC
- Objective criteria for endpoint determination
- Intention-to-treat primary analysis

25.0 PUBLICATION POLICY

The publication of results from any single center experience within the study is strongly discouraged until one year following the study's termination to allow for preparation and publication of the multicenter results.

26.0 REFERENCES

1. Yevzlin AS, Setum CM, Kallok MJ, Valliant A. Percutaneous AVG creation in a canine model. *Presented at the 2013 American Society of Diagnostic and Interventional Nephrology 9th Annual Scientific Meeting.*

2. Ebner, A, Ross JR, Setum CM, Kallok, MJ, Yevzlin AS. Transcatheter Anastomosis Connector System for Vascular Access Graft Placement: Results from a First-in-Human Pilot Study. *J Vasc Access* 2016; 17:111-117.