FLEX Vessel Prep Prior to the Treatment of Obstructive Lesions in the Native Arteriovenous Dialysis Fistulae (AVF)

Clinical Study Protocol

PROTOCOL NO.: VMG-2021-001

Clinical Study Plan	
Clinical Study Plan/Study Title	FLEX Vessel Prep prior to the Treatment of Obstructive Lesions in the Native Arteriovenous Dialysis Fistulae (AVF) NCT05034939
Study Product Name	FLEX Vessel Prep System (K202187)
Sponsor	VentureMed Group, Inc. 2800 Campus Drive, Suite 50 Plymouth, MN 55441
Document Revision	5

Protocol Approval – Sponsor and Principal Investigator

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Protocol Number: VMG-2021-001

Protocol Revision: **5**

Protocol Date: March 3, 2022

Device: FLEX Vessel Prep System

Protocol accepted and approved by:

Jill Schweiger Vice President, Clinical & Regulatory Affairs VentureMed Group, Inc.	March 3, 2022 Date
Principal Investigator (Printed Name)	
Principal Investigator (Signature)	Date

1 Contents

2 Definitions

Term	Definition
Access Circuit	The area from the AV access fistula arterial anastomosis to the axillosubclavian junction.
Access Thrombosis	A total occlusion within the AV access circuit due to thrombus formation which is rapidly evolving as confirmed by sudden onset of symptoms and documented by duplex ultrasound and/or angiography.
Arteriovenous “Dialysis” Fistulae (AVF)	The joining of an artery and vein for the purpose of hemodialysis access.
Clinical Success	Resumption of successful dialysis for at least one session after index procedure.
De Novo Lesion	A lesion that has not been previously treated.
Device Success	Successful delivery, treatment, and retrieval of the FLEX Vessel Prep System or the control device at index procedure.
Dissection Types A-F	Intimal disruption of the vessel wall with or without medial or adventitial contrast staining, classified as per the NHLBI (National Heart, Lung, and Blood Institute) criteria as follows: **A) Luminal Haziness**: Minor radiolucent areas in the lumen without impairment of flow or persistent dye staining after contrast runoff. **B) Linear Dissection**: Luminal flap that is radiolucent and that runs parallel to the vessel wall with contrast injection but without impairment of flow or persistent dye staining after contrast runoff. **C) Extraluminal Contrast (i.e., "cap dissection")**: Contrast appears outside of the vessel lumen as an "extraluminal cap." The staining appears even after contrast clears the lumen. **D) Spiral Dissection**: Spiral radiolucent luminal filling defects; often persistent staining after contrast clears from the vessel. **E) Dissection with Reduced Flow**: New and persistent filling defects in the vessel lumen **F) Dissection with Total Occlusion**: Lesions that progress to

Term	Definition
	impaired flow or total occlusion
Embolism	The obstruction of a blood vessel by a foreign substance or a blood clot that travels through the bloodstream, lodging in a blood vessel or plugging the vessel.
Enrollment	The time the guidewire has successfully crossed the lesion to be treated.
Optimal PTA	Repeated and prolonged balloon inflations aimed to achieve <50% residual stenosis (visual estimate) without stenting.
Procedural Success	Maintenance of patency (≤30% residual stenosis) in the absence of peri-procedural serious adverse event (SAE) involving the AV access circuit at 30 days post index procedure.
Bail-out Stenting	Placement of a stent due to sub-optimal PTA resulting in either of the following conditions: • Residual stenosis of ≥50% (by visual estimate); • Major (≥ Grade D) flow-limiting dissection.
Serious Adverse Event (SAE)	Adverse clinical event where the outcome is: **A) Death;** **B) Life-threatening event** (places subject at immediate risk of death from the experience as it occurred); **C) Hospitalization** (initial or prolonged) if admission to hospital was warranted as a result of an adverse event; **D) Disability or permanent damage** (substantial disruption of one's ability to carry out normal life functions); **E)** Congenital anomaly or birth defect; **F) Required interventions** to prevent permanent impairment or damage; or **G) Important medical event** that required medical or interventional treatment to prevent one of the previous outcomes, e.g. vascular perforation/rupture, embolism, extravasation, flow-limiting dissection, or hematoma necessitating treatment.
Steal Syndrome* Dialysis-associated steal syndrome (DASS)	Ischemic signs and symptoms (pain, diminished radial pulse, coldness, cyanosis, necrosis) produced by an access device as a result of the diversion of arterial blood flow into the AV fistula.

Term	Definition
Successful Dialysis	A complete dialysis session includes: • Normal cannulation *and* • Is not stopped prematurely.
Target Lesion Re-intervention (TLR)	Any repeat invasive procedure, including angioplasty, stenting or thrombolysis, performed to open or increase the lumen diameter within the previously treated lesion. ***Clinically-Driven Target Lesion Re-intervention (CD-TLR)***: Any re-intervention involving the target lesion in which: • The subject has a ≥50% diameter stenosis **in the presence of**clinical or physiologic abnormalities that indicate dialysis access dysfunction *OR* • ≥70% stenosis with or without the presence of clinical or physiologic abnormalities indicating dialysis access dysfunction. *Non-Clinically-Driven Target Lesion Re-intervention*: any re-intervention involving the target lesion which does not meet the criteria for CD-TLR.

** Defined by National Kidney Foundation KDOQI Guidelines*

3 Protocol Summary

Title	FLEX Vessel Prep prior to PTA for the Treatment of Obstructive Lesions in the Native Arteriovenous Dialysis Fistulae (AVF)
Clinical Study Type	Post Market Outcomes Research Study
Study Device	FLEX Vessel Prep System
Sponsor	VentureMed Group, Inc. 2800 Campus Drive, Suite 50 Plymouth, MN 55441
Study Purpose	To evaluate and compare the serious adverse event rate at 30 days and primary patency at 6 months when using FLEX Vessel Prep System prior to PTA vs. PTA alone for treatment of obstructive lesion of native arteriovenous fistulae in the upper extremity.
Primary Efficacy Endpoint	**Target Lesion Primary Patency Rate through 6 Months** Defined as freedom from clinically driven target lesion re-intervention (CD-TLR) or access circuit thrombosis measured through 6 months post-procedure.
Primary Safety Endpoint	**Serious Adverse Event Rate within 30 Days** Defined as the Serious Adverse Event (SAE) rate involving the AV access circuit through 30 days post-procedure.
Secondary Endpoints	**Secondary endpoints assessed through 6-months:** **Secondary Safety Endpoint: Serious Adverse Event Rate within 3 and 6 Months** Defined as the Serious Adverse Event (SAE) rate involving the AV access circuit through 3 months and 6 months post-procedure. **Access Circuit Primary Patency through 3- & 6- Months Post-procedure** Defined as freedom from re-intervention in the access circuit or access circuit thrombosis through 3 months and 6 months post-procedure. **Target Lesion Primary Patency through 3- & 6- Months Post-procedure** Defined as freedom from CD-TLR or access thrombosis occurring in the target lesion through 3 months and 6 months post-procedure. **Cumulative Target Lesion Reinterventions (TLR) Measured through 3- & 6-Months Post-procedure** Defined as proportion of subjects with TLR through 3 months and 6 months post-procedure.

Secondary Endpoints (Cont.)	**Number of Interventions Required to Maintain Target Lesion Patency through 3- & 6- Months Post-procedure** Defined as number of TLR through 3 months and 6 months post-procedure. **Number of Interventions Required to Maintain Access Circuit Patency through 3- & 6- Months Post-procedure** Defined as number of reinterventions in the target lesion and/or access circuit through 3 months and 6 months post-procedure. **Cumulative Access Circuit Thromboses Measured through 3- & 6-Months Post- procedure** Defined as proportion of subjects with access circuit thrombosis through 3 months and 6 months post-procedure. **Device Success**: Defined as successful delivery, treatment, and retrieval of the FLEX Vessel Prep device at index procedure. **Procedural Success**: Defined as maintenance of patency (≤30% residual stenosis) in the absence of peri-procedural serious adverse event (SAE) **Clinical Success**: Defined as resumption of successful dialysis for at least one session after index procedure. **Balloon opening pressure** Defined as minimum inflation pressure required to efface target lesion noting parallel balloon walls. **Maximum balloon pressure** of angioplasty balloon(s) required during the interventional procedure to treat target lesion. **Patient Reported Pain** During the interventional procedure reported via Numerical Rating Scale (NRS).
Study Design	A prospective, multi-center, randomized (1:1) clinical study evaluating the FLEX Vessel Prep device plus PTA (study arm) vs PTA alone (control arm) for the treatment of obstructive lesions in the native arteriovenous dialysis fistulae.
Sample Size	Up to 75 Subjects
Number of Sites	Up to 7 clinical sites in the United States.
Study Population	Subjects with a *de novo* or non-stented restenotic obstructive lesion up to 100 mm in length, located in the native arteriovenous dialysis fistulae in an upper extremity.

Inclusion Criteria	1. Patient is ≥21 years of age. 2. Patient has a life expectancy of ≥12 months. 3. Patient has a native AV fistula created ≥ 60 days prior to the index procedure. 4. The target AV fistula has undergone successful dialysis for at least 8 of 12 sessions during a four-week period. 5. Patient has a de novo and/or non-stented restenotic lesion located between approximately 2 cm proximal to the arteriovenous anastomosis and axillosubclavian junction with ≥50% stenosis. **Note**: If the lesion is located in the cephalic arch, the treatment may be delivered up to 2 cm into the subclavian vein. 6. Patient has a target lesion (which may include a tandem lesion) that is ≤ 100 mm in length (by visual estimate). **Note**: Tandem lesions may be enrolled provided they meet all the following criteria: • Separated from target lesion by a gap of ≤ 30mm (3 cm). • Total combined lesion length, including 30 mm gap, ≤ 100 mm. • Able to be treated as a single lesion. 7. Patient has a target vessel diameter of 4mm – 12mm (by visual assessment). 8. Patient underwent successful crossing of the lesion with the guidewire. 9. Patient provides written informed consent prior to enrollment in the study. 10. Patient is willing to comply with all follow-up evaluations at specified times.
Exclusion Criteria	1. Patient is pregnant or breastfeeding. 2. Patient is receiving immunosuppressive therapy. 3. Patient has undergone prior intervention of access site within 30 days of index procedure. 4. Patient with anticipated conversion to peritoneal dialysis. 5. Patient has an infected AV access or systemic infection. 6. Patient has planned surgical revision of access site. 7. Patient with secondary non-target lesion requiring treatment within 30-days post index procedure. 8. Patient with hemodynamically significant central venous stenoses that cannot be successfully treated prior to treatment of the target lesion. 9. Patient with target AVF or access circuit which previously had thrombectomy within last 30 days. 10. Patients judged to have a lesion that prevents complete inflation of an

	angioplasty balloon or proper placement of the delivery system. 11. Patient with target lesion located central to the axillosubclavian junction. 12. Patient has significant arterial inflow lesion requiring treatment more than 2 cm upstream from the anastomosis in the AV access. 13. Patient has presence of pseudoaneurysm or aneurysm requiring surgical revision at the target lesion site. 14. Patient with known contraindication, including allergic reaction, or sensitivity to contrast material that cannot be adequately pre-treated. 15. Patient who cannot receive recommended antiplatelet and/or anticoagulant therapy. 16. Patient with clinically significant Steal Syndrome requiring treatment. 17. Patient is enrolled in another investigational drug, device, or biologic study and has not completed the primary endpoint or was previously enrolled in this study. 18. Patient has a co-morbid condition that, in the judgment of the Investigator, may cause him/her to be non-compliant with the protocol or confound the data interpretation. 19. Patient has AV fistula created via endovascular technique.
Subject Follow-up	Subjects enrolled in the study will be followed up to 6 months. Follow-up assessments are scheduled for 30-days, 3- & 6-months post index procedure.
Time Course	Start of enrollment: June 2021. Completed enrollment: April 2022. Planned study close-out: approximately October 2022.

4 Background

In the United States there are approximately 468, 000 patients with end stage renal disease (ESRD) who require routine hemodialysis (HD) as their renal replacement therapy. Among prevalent patients as of December 2018, more than four out of every five patients receiving hemodialysis were using an AV fistula or graft (82.4%; 65.7% fistula and 16.7% graft[1]).

The natural history of a hemodialysis access is the persistent development of neointimal hyperplastic stenoses. In fistulas, the most common location of stenoses depends upon the type of fistula. Radial artery-cephalic vein fistulas often develop juxta-anastomotic stenoses, brachial artery to cephalic vein fistulas develop cephalic arch stenoses, often at the site of a hypertrophied valve ring and brachial artery to transposed basilic vein have a predilection to develop stenosis at the swing point of the vein.[2]

These stenoses cause a reduction in blood flow through the access and thereby decrease the ability to deliver effective hemodialysis treatment. If left untreated, these aggressive lesions will eventually cause the access to thrombose.

Percutaneous transluminal balloon angioplasty (PTA) is the primary technique for treatment of neointimal stenoses associated with prosthetic hemodialysis grafts and native fistulas. It remains the standard treatment to which other percutaneous techniques are compared.

Limitations of PTA include:

- Post angioplasty elastic recoil. After being dilated, elastic elements in the vessel wall cause immediate decrease in lumen diameter.
- Inability to fully dilate a lesion: Dense intimal hyperplasia can be resistant to expansion. Ultra-High-pressure balloons are needed which increase patient discomfort and the risk of vessel rupture.
- Recurrent stenosis.[3]

Although an angioplasty procedure can provide an excellent immediate result, the long-term patency rates are less than satisfactory with patients requiring an average 1.9 interventions per year.[4] Clinical studies describing the use of angioplasty to treat hemodialysis fistula-related stenoses have reported six-month patency rates of 25 – 78%.[5] Angioplasty failures may be due to acute elastic recoil, vascular rupture during balloon inflation or rapid re-growth of the neointimal stenosis. Subsequent dysfunction of the dialysis circuit is a significant cause of morbidity and mortality in patients undergoing HD which results in repeated interventions and can eventually lead to loss of vascular access.

The FLEX Vessel Prep™ system is currently marketed in the United States and cleared via 510K by the Food and Drug Administration (FDA). It is a vessel preparation device indicated for use with percutaneous transluminal angioplasty (PTA) catheters to facilitate dilation of stenoses in the femoral and popliteal arteries and treatment of obstructive lesions of native or synthetic arteriovenous dialysis fistulae. The device is also indicated for treatment of in-stent restenosis of balloon expandable and self-expanding stents in the peripheral vasculature. It is an over-the-wire sheathed system, utilizing a flexible vessel prep treatment element equipped with three flexible struts near the distal tip. The proximal portion of each flexible strut includes a 0.25mm micro-surgical blade. The FLEX Vessel Prep device is placed over an .014" or .018" guidewire distal to the lesion to be treated. The sheath is retracted, and the treatment element is expanded

to contact the lesion. A retrograde pull-back is applied to cross the lesion. The microsurgical blades on the proximal end of each treatment element strut independently engage in the lesion to create three parallel, circumferential continuous micro-incisions, with a depth of approximately 250 microns, along the entire length of the stenosis. The FLEX Vessel Prep treatment element is re-sheathed and advanced again through the lesion to allow a subsequent pullback.

Unlike static PTA balloons, the FLEX Vessel Prep™ System provides continuous engagement of the dynamic treatment element to create micro-incisions along the entire length of the stenosis. Creating longitudinal micro-incisions in the stenosis releases the circumferential tension to enable luminal gain with improved vessel compliance, may reduce the need for high pressure balloons and reduce vessel trauma and complications, including dissection and the need for bail-out stent placement.

Controlled vessel preparation with the FLEX Vessel Prep System may help minimize barotrauma of high-pressure balloon inflation and extend primary patency of the target lesion. Every step that can be taken to improve the outcomes in a patient population that has such limited options, fills a significant unmet clinical need.

5 Objectives and Endpoints

5.1 Primary Objective

To evaluate the 30-day SAE rate and primary patency rates using the FLEX VP System followed by PTA compared with PTA alone for treatment of subjects presenting with obstructive lesions of native arteriovenous dialysis fistulae(AVF) in the upper extremity.

5.2 Endpoints

5.2.1 Primary Endpoints

Primary endpoints for the study are as follows:

- Primary Efficacy Endpoint: Target Lesion Primary Patency Rate through 6 Months

Defined as freedom from clinically driven target lesion re-intervention (CD-TLR) or access circuit thrombosis measured through 6 months post-procedure.

- Primary Safety Endpoint: Serious Adverse Event Rate within 30 Days

Defined as the Serious Adverse Event (SAE) rate involving the AV access circuit through 30 days post-procedure.

5.2.2 Secondary Endpoints

Secondary endpoints assessed through 6-months (unless noted otherwise) for the study are as follows:

- Secondary Safety Endpoint: Serious Adverse Event Rate within 3 and 6 Months

  Defined as the Serious Adverse Event (SAE) rate involving the AV access circuit through 3 months and 6 months post-procedure.

- Access Circuit Primary Patency through 3 Months and 6 Months Post-Procedure

  Defined as freedom from re-intervention in the access circuit or access circuit thrombosis through 3 months and 6 months post-procedure.

- Target Lesion Primary Patency through 3 Months and 6 Months Post- Procedure

  Defined as freedom from CD-TLR or access thrombosis occurring in the target lesion through 3 months and 6 months post-procedure.

- Cumulative Target Lesion Reinterventions Measured through 3 Months and 6 Months Post-Procedure

  Defined as proportion of subjects with TLR through 3 months and 6 months post-procedure.

- Number of Interventions Required to Maintain Target Lesion Patency through 3 Months and 6 Months Post-Procedure

  Defined as number of TLR through 3 months and 6 months post-procedure.

- Number of Interventions Required to Maintain Access Circuit Patency through 3 Months and 6 Months Post-Procedure

  Defined as number of reinterventions in the target lesion and/or access circuit through 3 months and 6 months post-procedure.

- Cumulative Access Circuit Thromboses Measured through 3 Months and 6 months Post-procedure.

  Defined as proportion of subjects with access circuit thrombosis through 3 months and 6 months post-procedure.

- **Device Success**: Defined as successful delivery, treatment, and retrieval of the FLEX Vessel Prep device at index procedure.

- **Procedural Success**: Defined as maintenance of patency (≤30% residual stenosis) in the absence of peri-procedural Serious Adverse Event (SAE).

- **Clinical Success**: Defined as resumption of successful dialysis for at least one session after index procedure.

- **Balloon opening pressure** Defined as minimum inflation pressure required to efface target lesion noting parallel balloon walls.

- **Maximum balloon pressure** of angioplasty balloon(s) required during the interventional procedure to treat target lesion.

- **Patient Reported Pain** During the interventional procedure reported via Numerical Rating Scale (NRS).

6 Study Design

This is a prospective, multi- center, randomized (1:1) clinical study evaluating the FLEX Vessel Prep System followed with PTA (TEST arm) vs PTA alone (CONTROL arm) for the treatment of de novo or non-stented restenotic obstructive lesions up to 100 mm in length located in the arteriovenous dialysis fistulae in an upper extremity. Enrollment will continue until complete data sets are collected for up to 75 subjects from up to 7 sites in the US.

Once enrolled, subjects will remain in the study through completion of the required follow-up duration unless the subject withdraws consent, the subject expires, the investigator withdraws the subject, or VentureMed terminates the study for any reason. The enrollment phase is expected to take 3 months. The follow-up duration for each subject is up to 6 months. The total expected duration of the study is approximately 9 months.

7 Product Description

7.1 FLEX Vessel Prep™

The FLEX Vessel Prep System™ is an over-the-wire sheathed catheter with a three-strut treatment element near the distal tip. The Treatment Element consists of three independent flexible struts, each with a precision blade, mounted on the proximal end. As the device is pulled back in a retrograde fashion through the target lesion, the Treatment Element "flexes" providing continuous engagement along the lesion to create controlled depth microincisions.

7.2 PTA Balloon

The brand and type of PTA balloon(s) used will be at the discretion of the treating physician and used according to its IFU. PTA balloons consist of an over-the-wire catheter with a balloon fixed at the distal tip. Within the lesion the balloon is inflated to a pressure that allows full effacement. Standard pressure balloons (<20atm), high pressure (>20atm), and ultra-high pressure (>30atm) have been used for resistant AV stenosis.[6] Balloon sizing matches reference vessel diameter (RVD) 1:1 and usually extends beyond the lesion length.

8 Selection of Subjects

8.1 Study Population

This study will enroll subjects with a *de novo* or non-stented restenotic obstructive lesions up to 100 mm in length, located in the native arteriovenous dialysis fistulae in the upper extremity.

8.2 Inclusion Criteria

1. Patient is ≥21 years of age.
2. Patient has a life expectancy of ≥12 months.
3. Patient has a native AV fistula created ≥ 60 days prior to the index procedure.

4. The target AV fistula has undergone successful dialysis for at least 8 of 12 sessions during a four-week period.
5. Patient has a *de novo* and/or non-stented restenotic lesion located between approximately 2 cm proximal to the arteriovenous anastomosis and axillosubclavian junction with ≥50% stenosis.

   Note: If the lesion is located in the cephalic arch, the treatment may be delivered up to 2 cm into the subclavian vein.
6. Patient has a target lesion (which may include a tandem lesion) that is ≤ 100 mm in length (by visual estimate).

   Note: Tandem lesions may be enrolled provided they meet all of the following criteria:
   - Separated by a gap of ≤ 30mm (3 cm).
   - Total combined lesion length, including 30 mm gap, ≤ 100 mm.
   - Able to be treated as a single lesion.
7. Patient has a target vessel diameter of 4.0 – 12.0 mm (by visual estimate)
8. Patient underwent successful crossing of the target lesion with the guidewire.
9. Patient provides written informed consent prior to enrollment in the study.
10. Patient is willing to comply with all follow-up evaluations at specified times.

8.3 Exclusion Criteria

1. Patient is pregnant or breastfeeding.
2. Patient is receiving immunosuppressive therapy.
3. Patient has undergone prior intervention of access site within 30 days of index procedure.
4. Patient with anticipated conversion to peritoneal dialysis.
5. Patient has an infected AV access or systemic infection.
6. Patient has planned surgical revision of access site.
7. Patient with secondary non-target lesion requiring treatment within 30 days post index procedure.
8. Patient with hemodynamically significant central venous stenoses that cannot be successfully treated prior to treatment of the target lesion.
9. Patient with target AVF or access circuit which previously had thrombectomy within last 30 days.
10. Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system.
11. Patient with target lesion located central to the axillosubclavian junction.
12. Patient has significant arterial inflow lesion requiring treatment more than 2 cm upstream from the anastomosis in the AV access.
13. Patient has presence of pseudoaneurysm or aneurysm requiring surgical revision at the target lesion site.
14. Patient with known contraindication, including allergic reaction, or sensitivity to contrast material that cannot be adequately pre-treated.

15. Patient who cannot receive recommended antiplatelet and/or anticoagulant therapy.
16. Patient with clinically significant Steal Syndrome requiring treatment.
17. Patient is enrolled in another investigational drug, device, or biologic study and has not completed the primary endpoint or was previously enrolled in this study.
18. Patient has a co-morbid condition that, in the judgment of the Investigator, may cause him/her to be non-compliant with the protocol or confound the data interpretation.
19. Patient has AV fistula created via endovascular technique.

9 Study Procedures

9.1 Schedule of Events

Table1 provides an overview of the assessment requirements for the study.

Table 1: Study Assessment Requirements

Assessment/ Procedure	**Baseline/ Screening** (within 30 days of procedure)	**Index Procedure**	**Discharge** (within 7 days post-procedure)	**30 Days** (± 7 days)	**3 Months** (90 ± 15 days)	**6 Months** (180 ± 30 days)	**Unscheduled Visit**	**Target AVF Abandon-ment**
Informed Consent	X							
Medical History	X							
Physical Exam	X						X	
Medication Assessment	X	X	X					
Numeric Rating Scale	X	X						
Angiography		X					X*	
Randomization		X						
Serious Adverse Event Collection		X	X	X	X	X	X	X
Abandonment of Fistula								X

* Collect if revascularization required.

9.2 Subject Consent

All subjects must undergo the consent process, possess the mental capacity to provide Informed Consent, and sign the ICF prior to enrollment and prior to undergoing any assessments or procedures that are study-specific (defined as those that would not be conducted if the subject were not participating in the study).

The ICF and other written explanatory information will be revised if significant new information that may be relevant to the subject's consent becomes available, or there is an amendment to the protocol which necessitates a change to the ICF. The subjects should be re-consented in a timely manner and will be asked to confirm willingness to continue his/her participation in the study and obtain his/her signature (with printed name) on the revised consent form. All revisions to the consent form must be approved in advance by the IRB.

9.3 Baseline Evaluation

As part of the screening process, subjects will undergo a standard physical exam including a physical examination of the target limb and medical history (review of symptoms, pre-existing conditions, and medications). The baseline review will also capture information on the target AVF (location, age, and previous re-interventions). A Numeric Rating Scale (NRS) will be collected to assess pain at the access site. Although not required by the protocol, any laboratory tests/results performed by the treating physician as part of standard care to evaluate the patient will be collected.

9.4 Index Percutaneous Intervention Procedure – Prior to Randomization

- During and after the procedure, the appropriate anti-coagulants, anti-platelet agents and vasodilators should be administered to the patient according to the institutional practice.
- A pre-enrollment fistulogram is performed to assess whether the subject meets the anatomic eligibility criteria for the target lesion per section 8.
- Cross the lesion with a guidewire.

9.5 Subject Enrollment and Randomization

A subject will be enrolled in the study after he/she has signed the informed consent, it has been determined that he/she meets all the inclusion criteria and none of the exclusion criteria, and the guidewire has successfully crossed the lesion selected for treatment. If the lesion cannot be crossed, it will be classed as a screen failure. All information collected up until the point of screen failure, including the informed consent form, demographics, and procedure information, will be stored in a Screening Binder.

Once the patient is enrolled, they will be randomized in a 1:1 fashion into the TEST Arm or CONTROL Arm by using sealed envelopes. Randomization will follow a permuted block design and be stratified by site. After confirming the lesion can be crossed with the guidewire, the

site will open the envelope that is next in sequence and assign the corresponding Subject ID number. Envelopes containing the randomization assignment and Subject ID number (beginning with 001) will be stored in the Subject Binder.

9.6 Index Percutaneous Intervention Procedure – After Randomization

9.6.1 TEST Arm: FLEX Vessel Prep™ System and PTA

- FLEX Vessel Prep is placed over an 0.14" or 0.18" guidewire and advanced distal to the lesion to be treated. Following procedural guidelines in the Instructions for Use, the FLEX Vessel Prep System is used to create circumferential, continuous micro-incisions along the length of the stenosis by performing a retrograde pullback through the lesion.
- Post use of the FLEX Vessel Prep, a fistulogram of the AV access circuit is obtained.
- Standard Balloon angioplasty is performed with an uncoated PTA balloon sized to meet the reference vessel diameter, according to its corresponding instructions for use. Once advanced to the lesion, the balloon should be inflated according to the site's standard of care.
    - Note 1: During balloon inflation, **opening/effacement pressure** (defined as minimum inflation pressure required to efface target lesion noting parallel balloon walls) and **maximum pressure** (defined as highest pressure required during index procedure to treat target lesion) will be assessed.
    - Note 2: Administer the NRS to the subject to identify the highest level of pain experienced during the procedure.
- A fistulogram is obtained of the final PTA result.
- Record procedural data on the CRFs.

9.6.2 CONTROL Arm: PTA

- Optional: A standard uncoated PTA balloon is sized to meet the reference vessel diameter, according to its corresponding instructions for use. The balloon is placed over an appropriate guidewire and advanced to the lesion. The balloon is inflated to pre-dilate the lesion according to its instructions for use and the site's standard of care.
    - Note 1: During balloon inflation, **opening/effacement pressure** (defined as minimum inflation pressure required to efface target

lesion noting parallel balloon walls) and **maximum pressure** (defined as highest pressure required during index procedure to treat target lesion) will be assessed.

- Post pre-dilation, a fistulogram of the AV access circuit is obtained.
- Standard Balloon angioplasty is performed with an uncoated PTA balloon sized to meet the reference vessel diameter, according to its corresponding instructions for use. Once advanced to the lesion, the balloon should be inflated according to the site's standard of care.
    - Note 1: During balloon inflation, **opening/effacement pressure** (defined as minimum inflation pressure required to efface target lesion noting parallel balloon walls) and **maximum pressure** (defined as highest pressure required during index procedure to treat target lesion) will be assessed.
    - Note 2: Administer the NRS to the subject to identify the highest level of pain experienced during the procedure.
- A fistulogram is obtained of the final PTA result.
- Record procedural data on the CRFs.

9.6.3 Stent Placement

Placement of a stent or stent graft should be avoided unless required for subject safety.

Stent placement should be performed only after repeated and prolonged balloon inflations result in either of the following conditions:

- Residual stenosis of ≥50% (by visual estimate)
- Major (≥ Grade D) flow-limiting dissection

All subjects who undergo a stenting are required to be followed per the protocol-required follow-up schedule.

9.6.4 Discharge

All subjects will be evaluated for serious adverse events (SAEs) and complications prior to discharge.

9.7 Follow-up Requirements

The subject will followed after 30 days, 3 months and 6 months post procedure.

The following assessments will be performed during these follow-ups:

- Evaluation for SAE's
- Patency of Access Site
- Access Circuit Reintervention Information

If the access site used in the study is abandoned, the subject should be withdrawn from the study.

9.8 Unscheduled Visit

A subject who returns to the investigational site between protocol-required follow-up for a clinical event in the target limb is considered to have an Unscheduled Visit. A physical examination and evaluation for SAEs will be completed and recorded on the appropriate CRFs. Angiography and/or duplex ultrasound should be repeated if clinically indicated and/or within the institution's standard of care.

9.9 Data Collection

9.9.1 Source Documents

Data recorded onto paper case report forms (CRF) must be traceable to source documents. Source documentation is defined as the first-time data appears and may include original documents, data, and medical records (e.g., hospital records, clinical and office charts, laboratory notes, etc.).

9.9.2 Deviation Handling

A deviation is any event in which the study is not conducted according to the protocol, applicable laws or regulations or the Investigator Agreement. Deviations may include, but are not limited to the following:

- Failure to obtain informed consent prior to participation
- Incorrect version of the informed consent form used
- Failure to obtain IRB approval before enrolling subjects in the study
- Included subject did not meet inclusion/exclusion criteria
- Required testing and/or measurements not done or incorrectly done
- Subject missing a required follow-up
- Follow-up was completed outside window
- Source data permanently lost
- Enrollment of subjects during lapse of IRB approval

Reporting of all deviations should comply with IRB policies and must be reported to VentureMed as soon as possible upon the site becoming aware of the deviation. All deviations will be documented.

9.9.3 Subject Withdrawal or Discontinuation

Every subject should be encouraged to remain in the study until they have completed the required follow-up per the protocol, however subjects have the right to withdraw their consent to participate at any time during the study. Withdrawal of a subject from the study can also occur at the direction of the Principal Investigator without the subject's consent for any reason.

If a subject expires, has the access site abandoned, withdraws early, or is withdrawn from the study early by the Investigator, the reason for withdrawal must be recorded in the subject's medical record and on the Exit Form.

9.9.4 Loss to Follow-Up

Every attempt should be made to have all subjects complete the follow up schedule. A subject will be considered lost-to-follow-up after three documented unsuccessful attempts to make contact (phone, email, text, or mail). Once deemed lost-to-follow- up, the communication efforts must be recorded in the subject's medical record and on the Exit Form.

10 Risks and Benefits

10.1 Potential Risks

This is a post-market study in which the risks to subjects are no greater as a result of study participation. Potential risks or complications anticipated with the use of the market-released FLEX Vessel Prep System, catherization procedure, and market-released PTA include, but may not be limited to, those listed in the Instructions for Use of the Test and Control devices.

Subjects will be informed of any significant new findings that develop during the course of the study that may affect their willingness to continue participation. The Investigator will oversee all safety aspects of the study and report all adverse events to the IRB.

10.2 Potential Benefits

There are no guaranteed benefits from participation in the study. It is possible that treatment with the FLEX Vessel Prep System prior to use of PTA may improve and maintain blood flow through the treated AVF, resulting in the need for fewer treatments. This may allow for continued/resumption of AV access for the purpose of hemodialysis. Additionally, it is possible that lower balloon inflation pressures following FLEX Vessel Prep use will result in fewer complications and potentially less pain experienced during the procedure. Information gained from the conduct of this study may be of benefit to other persons with the same medical condition.

11 Serious Adverse Event Assessments

The Investigator is required to assess and document in the medical record all Serious Adverse Events (SAEs) observed in subjects from the time of enrollment until the event resolves or the subject exits the study. In cases in which SAEs are unresolved at the time of study exit, this will be documented on the CRF.

The Investigator is responsible for reporting SAEs to VentureMed as soon as possible, but no later than 10 working days after the Principal Investigator is first aware of the event, by completing the Adverse Event CRF. The Principal Investigator is responsible for reporting the SAE to the IRB as applicable.

12 Statistical Design and Methods

This is a prospective, multicenter, randomized (1:1) study of FLEX Vessel Prep prior to PTA vs PTA alone for the treatment of de novo and non-stented restenotic lesions in the AVF. The study will enroll at up to seven centers in the US.

Comparison of binomial proportions will be performed using Fisher's exact test. Time-to-event analyses using the Kaplan-Meier method may be conducted to supplement the primary analysis of proportions. Comparisons of continuous variables will be performed using a two-sample t-test or Wilcoxon rank-sum test.

For the primary efficacy endpoint and other 6-month endpoints that compare the proportion of subjects between arms, the numerator is the number of subjects with an event within 6 months and the denominator is the number of subjects with an event or who were followed for at least 150 days.

For the primary safety endpoint and other 30-day endpoints that compare the proportion of subjects between arms, the numerator is the number of subjects with an event within 30 days and the denominator is the number of subjects with an event or who were followed for at least 23 days.

The primary analysis will be based on intent-to-treat, including all subjects with available follow-up data analyzed by the arm to which they were randomized. Two-sided p-values less than 5% and one-sided p-values less than 2.5% will be considered statistically significant. For this post-market study, statistically significant differences are not anticipated. The study is intended to provide estimates of the differences between groups. Estimated differences and their 95% confidence intervals will be reported for all endpoints. For the primary efficacy endpoint, if primary patency rates are 60% and 80% in the control and treatment arms respectively, the 95% confidence interval width will be approximately ±25%. For the primary safety endpoint, if SAE rates are 5% in both arms, the 95% confidence interval width will be approximately ± 17%.

Further details on the statistical methods, including justification, timing of interim analysis can be found in the Statistical Analysis Plan.

13 Ethics

The study will be conducted according to the study protocol, Clinical Trial Agreement, and all federal,

regulations, standards, and requirements including: 21 CFR Parts 11, 50, 54, 56, and 45 CFR part 46.

The clinical site will not begin enrolling subjects until the required approval/favorable opinion from the IRB has been obtained.

The site must provide VentureMed with a copy of the investigational site's IRB approval letter and the IRB-approved Informed Consent Form. If applicable, approvals for the continuation of the study must be kept current in accordance with the IRB's review schedule. All site communications to and from the IRB must be forwarded to VentureMed as they are sent/received.

VentureMed will be informed by the IRB and/or the Investigator in case any action is taken by an IRB with respect to this investigation.

This study was publicly registered on www.clinicaltrials.gov prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA).

14 Study Administration

14.1 Investigator Responsibility / Performance

The Investigator is responsible to ensure that all work and services related to this study described herein, or incidental to those described herein, are conducted in accordance with the highest standards of medical and clinical research practice, the requirements of the IRB, the protocol,and the terms of the Clinical Trial Agreement, and all applicable regulations.

The Investigator must maintain a Delegation of Authority Log of appropriately qualified persons to whom the Investigator has delegated significant study related duties.

14.2 Monitoring

Monitoring and monitoring oversight will be provided by VentureMed (i.e., contractors and authorized designees).

VentureMed will be responsible for ensuring adequate monitoring, including site initiation and study closure, to ensure the protection of the safety and rights of subjects, as well as the quality and integrity of the data collected and submitted. Frequency of monitoring will be based upon enrollment, study duration, site compliance, and any suspected inconsistency in data that requires investigation. After each monitoring visit, the monitor will send the Principal Investigator a letter summarizing the monitoring visit. The Principal Investigator will be responsible for ensuring that follow-up actions needed to resolve issues are completed in an accurate and timely manner.

When source data verification is performed, the monitor must be granted direct access to original source documentation or certified copies of the original source must be provided. Direct access must also be permitted for individuals conducting audits, IRB review and regulatory inspections.

If electronic source documentation is used at the site, the site must provide to the monitor:

- Direct access to the electronic medical record (e.g., the monitor is given a guest passwordto directly access the system) or
- Direct access to the electronic medical record by reviewing alongside appropriate study staff (e.g., a research coordinator).

14.3 Data Management

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject device.

Study personnel at the site will enter data from source documents corresponding to a subject's visit/follow-up into the protocol-specific paper in a timely manner. Subjects will not be identified by name in the study database or on any study documents to be collected by the VentureMed (or designee) but will be identified by a site number and subject number.

If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data, and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

It is recommended that all data is completed and sent to VentureMed within 10 business days of the completion of the protocol-specified assessments or sooner as requested by VentureMed.

14.4 Data Queries

During the review of source documents and CRFs at the monitoring visits, any discrepancies noted will be queried by VentureMed or its designee and must be resolved by the site staff and Investigator in a timely manner. In addition, VentureMed, or its designee, may also generate data queries during routine or remote review of the data. These queries will be sent to the site and must also be resolved in a timely manner.

14.5 Confidentiality

Subject confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique subject identification code consisting of the unique Site Number and Subject Number will be assigned and used to allow identification of all data reported for each subject.

To maintain confidentiality, the subject's name should not be recorded on any study document other than the informed consent form. This scenario will be covered in the Patient Informed Consent Form. In the event a subject's name/PHI is included for any reason, it will be redacted as applicable. In the event of inability to redact the identification (e.g., digital

media), it will be handled in a confidential manner by the authorized personnel.

Study data may be made available to third parties, e.g., in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed.

The identity of a subject will never be disclosed if study data are published.

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

14.6 Investigator reports

The Investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events, deaths, and any deviations from the protocol. If any action is taken by an IRB with respect to this clinical study, copies of all pertinent documentation must be forwarded to VentureMed in a timely manner. Reports are subject to inspection and to the retention requirements as described above for Investigator records.

If any action is taken by an IRB with respect to this clinical study, copies of all pertinent documentation must be forwarded to VentureMed in a timely manner.

Table 2: Investigator Reports per VentureMed Requirements

Report	Submit to	Description/Constraints
Withdrawal of IRB approval (or lapse in IRB approval)	Sponsor	The Investigator must report a withdrawal of approval by the reviewing IRB of the Investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and IRB	Prior approval is required for changes in the plan or deviations. All deviations should be reported to VentureMed group and IRB (as required) in a timely manner.
Progress report	Sponsor and IRB	The Investigator must submit a progress report to the sponsor and IRB at regular intervals, but in no event less than yearly.
Failure to obtain informed consent prior to enrolling patients into the study	Sponsor and IRBs	If an Investigator enrolls a patient into the study without obtaining informed consent, the Investigator shall report such use within 5 working days after enrollment.

14.7 Suspension or Early Termination

VentureMed may decide to suspend or prematurely terminate the clinical study (e.g., if information becomes available that the risk to study subject is higher than initially indicated). If the clinical study is terminated prematurely or suspended, VentureMed shall promptly inform the Investigator of the termination or suspension and the reason(s) for this. The Investigator shall then promptly inform the reviewing IRB and study subjects.

15 References

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[3] Juan C. Duque, Marwan Tabbara, Laisel Martinez, Jose Cardona, Roberto I. Vazquez-Padron, Loay H. Salman. Dialysis Arteriovenous Fistula Failure and Angioplasty: Intimal Hyperplasia and Other Causes of Access Failure. American Journal of Kidney Diseases. Volume 69, Issue 1, 2017, Pages 147-151,ISSN 0272-6386.

[4] Litchfield, T. Dialysis Access Coding Essentials, Recent Changes and Location Distinctions. Endovascular Today June 2019. Vol.18. No. 6.

[5] Liao M-T, Chen M-K, Hsieh M-Y, Yeh N-L, Chien K-L, Lin C-C, et al. (2020) Drug-coated balloon versus conventional balloon angioplasty of hemodialysis arteriovenous fistula or graft: A systematic review and meta-analysis ofrandomized controlled trials. PLoS ONE 15(4): e0231463.

[6] Trerotola SO, Stavropoulos SW, Shlansky-Goldberg R, et al. Hemodialysis-related venous stenosis: Treatment with ultra-high-pressure angioplasty balloons. Radiology 2004;231(1):259-262.