Protocol Synopsis

Study Title & ID	**I**ntravascular Ultrasound-**Guide**d Intervention for Venous Leg **U**lcers (IGuideU) Protocol ID: 200202
Objectives	The primary objective of this study is to determine whether the interrogation of the deep venous system (iliac-common femoral veins) for deep venous obstruction (DVO) by multiplanar venography (MPV) plus intravascular ultrasound (IVUS), with subsequent interventional treatment *determined and guided* by IVUS (interrogation group), results in improved clinical outcomes when compared to deferred interrogation of the deep venous system (deferred-interrogation group). The secondary objectives are to assess changes in treatment decision parameters made with MPV after further investigation with IVUS and to assess the long-term clinical and economic impact of IVUS-guided interventional treatment for venous leg ulcers compared to the deferred-interrogation group.
Study Design	Global, prospective, multi-center, randomized controlled trial. After signing a written informed consent, patients will be randomized 1:1 to either a deferred-interrogation group or to an interrogation group in which patients will be first evaluated with MPV imaging during iliac-common femoral vein assessment for possible endovascular intervention and then further interrogated with IVUS imaging. The treatment plan derived from venography alone will be compared to the treatment plan created with the addition of the IVUS information and any differences in treatment plan will be documented. Confirmation of whether or not the threshold of stenosis/occlusion required for endovenous stenting has been met will be determined by the IVUS imaging obtained. Any patients determined to require venous stenting will be stented according to the on-label manufacturer's instructions for the use of IVUS in guiding stent sizing and placement. This study will employ an independent core laboratory to evaluate, review and adjudicate all scheduled and unscheduled de-identified wound, MPV, and IVUS images. The study will also utilize a medical monitor to review and adjudicate peri-procedural serious adverse events (SAE).
Endpoints	Primary Clinical Endpoint The primary clinical endpoint is the difference in complete ulcer healing between the interrogation group and the deferred-interrogation group at 3 months. Complete ulcer healing is defined as 100% epithelialization of the venous ulcer. Healing will not be assumed for any area of the wound where a scab is present. Diagnostic Endpoint The diagnostic endpoint is a composite of the difference in DVO detection and the subsequent changes in treatment plan created based on the IVUS information in combination with MPV information versus the initial treatment plan created using the information from MPV alone. DVO is defined as ≥50% diameter reduction in the deep venous system when assessed by MPV or ≥50% reduction in cross-sectional area (CSA) of the deep venous system when assessed by IVUS. Changes in the following parameters will be considered a changed in treatment plan: 1. Location of the IVC confluence (common iliac vein/confluence interface) relative to vertebral bodies 2. Presence of significant disease (≥50% reduction in diameter and/or cross-sectional area) 3. Location of the disease

	4. Percentage (%) of obstruction/compression (compression or residual lumen diameter divided by reference vessel diameter) 5. Reference vessel and associated diameter/CSA 6. Length of disease (mm) 7. Decision to stent 8. Decision to pre- and/or post-dilate the occlusion 9. Number of stents to be used 10. Length(s) and Diameter(s) of stents to be used 11. Manufacturer and model of stent(s) to be used 12. Desired landing zones for stent placement 13. Diagnosis of PTS, NIVL, or other <u>Secondary Endpoints</u> The following are secondary endpoints: 1. Rate of ulcer healing measured between groups at 3, 6, 12, 18 and 24 months. 2. Rate of ulcer healing for stented PTS and NIVL patients at 3, 6, 12, 18 and 24 months. 3. Recurring ulcers in both arms from 3 months out to follow-up visit 24 months provided each arm has at least 30 subjects. The choice of 30 is based on central limit theorem in order to have normally distributed data for descriptive summary statistics. 4. Recurring ulcers between PTS and NIVL sub-groups. 5. Change in QoL using EQ5D and SF-36 forms. 6. Change in clinical score will be assessed using the VCSS and CEAP scoring systems. 7. Medical resource utilization (MRU) and health economic analysis between the interrogation and deferred-interrogation arms. *Note: Every effort will be made to balance the enrollment of PTS and NIVL patients.
Subject Population	In order to have 212 evaluable subjects with a 20% projected attrition rate, up to 266 evaluable subjects will be enrolled and randomized. *Inclusion Criteria:* 1. Be ≥ 18 and ≤ 85 years of age. 2. Able and willing to participate and comply with the protocol, including the defined follow-up schedule, by signing an IRB or Ethics Committee approved informed consent form. 3. Active venous leg ulcer (CEAP C6). 4. Previously completed treatment for clinically significant reflux in the superficial and/or perforator venous system of the target limb ≥ 3 months prior to enrollment, if clinically indicated. 5. Completed at least 3 months of prescribed compression therapy *after* any ablation. 6. Palpable dorsalis pedis or posterior tibial artery (DP/PT) pulses at ipsilateral foot or ABI ≥0.8. 7. Be able to ambulate unassisted or with non-motorized assistive devices. 8. Current VLU present ≤ 48 months. *Exclusion Criteria:* 1. Patient is known pregnant or breast-feeding or planning to become pregnant in the following year. 2. If antiplatelet and anticoagulation therapy cannot be tolerated. 3. Previous venous stent implantation involving the target limb, target lesion, or inferior vena cava. 4. Previous venovenous bypass surgery involving the target limb. 5. Previous endovascular recanalization of the target lesion segment 6. Known metal allergy precluding stent implantation.

	7. Known or suspected to have inadequate inflow to support stent patency in the target limb. 8. Active cancer diagnosis. 9. Known positive test for COVID-19 (Sars-CoV-2) within the last 2 weeks ***and*** actively symptomatic. 10. Known or suspected venous outflow obstruction caused by tumor compression/encasement with or without thrombus. 11. Known allergy to contrast media that cannot adequately be pre-medicated prior to study procedure. 12. Known Renal dysfunction (defined as eGFR <30 mL/min/1.73m^2) that would preclude adequate contrast usage. 13. Diagnosed with right heart failure/pulmonary hypertension. 14. Has known clinically significant abnormal platelet count outside laboratory reference ranges. 15. Has known clinically significant abnormal WBC, fever, sepsis or positive blood culture. 16. Organ transplant requiring immunosuppressant therapy. 17. Unstable angina pectoris, or myocardial infarction within 30 days and/or hemorrhagic stroke within 3 months. 18. Subjects with an active diagnosis of osteomyelitis of the ipsilateral limb. 19. Previous or planned surgical or catheter-based procedure on index leg within 30 days before or 30 days after the index procedure. 20. Active participation in another investigational drug or device study. 21. Subject has any condition, which, in the opinion of the investigator, precludes the subject from participation.
Test Groups	• Deferred-Interrogation Group: See guidelines below. • Interrogation Group: Compression therapy plus endovascular imaging (MPV+IVUS) with or without intervention (stenting). The deferred-interrogation group will continue to receive non-invasive therapies consisting primarily of compression therapy/stockings that would have otherwise been continued outside of this research protocol. Listed below are the protocol guidelines for deferred-interrogation therapies: **Mandate** • Continued compression therapy/dressing as prescribed. **Allow** • Periodic leg elevation. • Sclerotherapy under ulcer bed. • Recommend mechanical debridement as needed. • Wound biopsy if evidence of infection. • Systemic antibiotics if patient is diagnosed with an infection, avoid prophylactic prescription. • Pain management medication (Pentoxifylline/Trental) allowed but not recommended • Topical antimicrobial as needed. **Prohibit** • Negative pressure systems. • Artificial and/or autologous skin grafting within first 3 months after randomization and within the first 3 months for subjects that crossover from the deferred-interrogation group to the interrogation group. • Skin substitutes and tissue-based therapies within first 3 months after randomization and within the first 3 months for subjects that crossover from the deferred-interrogation group to the interrogation group. • Experimental topical creams and lotions.

- Growth factors within first 3 months after randomization and within the first 3 months for subjects that crossover from the deferred-interrogation group to the interrogation group.

Schedule of Assessments

There are 6 in-person visits planned for this clinical study, including the screening visit. The study is anticipated to last a total of 24 months for each enrolled study	Screening Visit	Baseline Visit/Index Procedure	1 Month (30 days)	3 Months (90 days)	6 Months (180 days)	12 Months (365 days)	18 Months (545 days)	24 Months (720 days)	Early Termination Visit*	Unscheduled Visit*	Re-intervention Procedure*
Visit Window	-30 to 0 days	0 days	±14 days	±14 days	±30 days	±30 days	±30 days	±30 days	NA	NA	NA
Visit Type	Office	Hospital /OBL	Office	Office	Office	Office	Phone Call	Phone Call	Office/ Hospital/ OBL	Office/ Hospital /OBL	Hospital /OBL
Informed Consent	X										
Medical History	X										
Eligibility/Inclusion and Exclusion Criteria	X										
Urine Pregnancy Test[a]		X									
Enrollment and Randomization	X										
Duplex Ultrasound[b]			X	X	X	X					
Physical examination	X		X	X	X	X			X	X	
Anticoagulant and Antiplatelet	X	X	X	X	X	X	X	X	X[h]	X[h]	X[h]
Clinical Laboratory Tests[c]		X									
Venous Ulcer Assessment	X	X	X	X	X	X			X[h]	X[h]	X[h]
Venous Ulcer Imaging		X	X	X	X	X			X[h]	X[h]	X[h]
CEAP Clinical Category	X	X	X	X	X	X			X[h]	X[h]	X[h]
VCSS Category	X	X	X	X	X	X			X[h]	X[h]	X[h]
Study Visit Questionnaire			X	X	X	X			X[h]	X[h]	X[h]
Wound Care Management Education[d]		X	X	X	X	X					
SF-36		X							X[h]	X[h]	X[h]
EQ5D Questionnaire		X							X[h]	X[h]	X[h]
Phone Call Questionnaire							X	X			
MPV Imaging[e]		X									

	IVUS Imaging[e]		X									
	Adverse Events[f]		X									
	Patient-completed Diary[g] SF-36 Questionnaire[i] EQ5D Questionnaire[i]	Completed monthly for study duration, through 24 months										

Abbreviations: CEAP - Clinical Etiology Anatomy Pathology, EQ5D – EuroQol 5 Dimensions; IVUS – intravascular ultrasound, MPV – multi- planar venography, SF-36 – Short form 36; VCSS – Venous Clinical Severity Score.
*Note: While an attempt should be made to collect all non-invasive testing at unscheduled visits, early termination visits, or re-interventions, a protocol deviation will not be required if all assessments are not completed.
[a]Urine pregnancy test shall be taken on all females of childbearing prior to the index procedure.
[b]In all follow-up visits, DUS will be performed on the patients who received a stent implantation as part of the index procedure to assess stent patency and position.
[c]Clinical laboratory tests include: Serum creatinine and eGFR. These laboratory tests must be performed within 30 days of the index procedure.
[d]Study personnel will provide guidance on wound care management best practices according to the site/facility guidelines.
[e]MPV and IVUS imaging will only be performed on patients receiving an index-procedure per the study protocol.
[f]Adverse Event reporting is for peri-procedural events and IVUS-related adverse events (<48 after index-procedure).
[g]Subjects will be provided with a diary at the baseline visit. The diary is designed to be completed on a monthly basis, as well as following any contact with the health care system related to treatment of his/her venous leg ulcer. The diary will be used to track major events, such as compliance to compression therapy and other notes related to the index ulcer. The diary also requires completion of the quality-of-life questionnaires (EQ-5D, SF-36). The diary will be reviewed at each office visit after the initial receipt. After the last in-person study visit, any hard-copy diaries will be sent to the study site coordinator on a monthly basis until the 24-month study completion.
[h]For early termination, unscheduled follow-up visits, and/or re-intervention procedures every attempt should be made to obtain the following assessments: Antiplatelet and Anticoagulant use; Study Visit Questionnaire; Venous Ulcer Assessment including venous ulcer imaging; CEAP clinical category, VCSS category, and the SF-36 and EQ5D Questionnaires.
[i] Questionnaires should be completed in the diary. If not completed in the diary, the subject should complete the questionnaires at the time of the visit.
[j] Screening and baseline visits can be combined

At-Home Subject Procedures	• Diary of compliance with standard of care procedures, wound care management, quality of life questionnaires, and medical resource use questions. • Follow-up phone call at 18 and 24 months.

Study Schematic

The following diagram illustrates the sequence of evaluations and follow-up visits for study participants: