Study Name

The LAVA Study

Study Number

TPR-00913-01.A

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Study Title

Liquid Embolization of Arterial Hemorrhages in Peripheral Vasculature (The LAVA Study)

Clinical Investigation Plan

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Liquid Embolization of Arterial Hemorrhages in Peripheral Vasculature

The LAVA Study

BlackSwan VASCULAR

Lava™ Liquid Embolic System

[redacted]

IDE Number: G190291

Sponsor

BlackSwan Vascular, Inc.

[redacted]

[redacted]

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SYNOPSIS

Protocol Number:	TBD
Investigational Device:	Lava™ Liquid Embolic System (LES)
Study Title	Liquid Embolization of Arterial Hemorrhages in the Peripheral Vasculature The LAVA Study
Sponsor	BlackSwan Vascular, Inc. [redacted]
Study Purpose	To evaluate the safety and effectiveness of the Lava LES for the embolic treatment of arterial hemorrhage in the peripheral vasculature.
Study Population	113 enrolled subjects
Number of Sites	Up to 20 investigational sites in the United States; no more than 25 subjects will be enrolled at any single site
Study Design	Prospective, multicenter, single-arm study of the Lava LES for the embolic treatment of arterial hemorrhage in the peripheral vasculature.
Primary Endpoints	Primary Safety Endpoint: The primary safety endpoint is a composite of freedom from 30-day Major Adverse Events (MAEs). MAEs include the following events as adjudicated by an independent Clinical Events Committee (CEC): 1. Ischemia or infarction of the target territory; 2. Non-target embolization; 3. Allergic reactions to Lava; 4. Catheter breakage; 5. Catheter entrapment defined as the inability to withdraw a catheter from adherence to Lava. Primary Effectiveness Endpoint: The primary effectiveness endpoint is Clinical Success, defined as absence of bleeding from the target lesion after embolization with the Lava LES, without the need for emergency surgery, re-embolization, or other target lesion reinterventions within 30 days of the index procedure. Absence of bleeding is defined as no BARC Type 3 or greater bleeding occurring after the index procedure, either persistent or recurrent. The ascertainment of persistent or recurrent BARC Type 3 or greater bleeding does not include bleeding that occurred prior to the conclusion of the index procedure. The primary effectiveness endpoint will be adjudicated by the CEC, relying on information from the source documents and/or core laboratory findings of absence of bleeding. Effectiveness relates to the target lesion(s) as defined by the Investigator at the index procedure.

Secondary Endpoints	The following measures will be assessed as secondary endpoints of the study: 1. Assessment of each element of the primary safety endpoint (MAE) as an individual component; 2. Symptomatic ischemia in the target territory that does not require intervention; 3. All-cause mortality; 4. Bleeding-related mortality (attributable to bleeding in a target territory); 5. Open surgical conversion for persistent or recurrent bleeding; 6. Device-related serious adverse events; 7. Procedure-related serious adverse events; 8. Access site hematoma (>5cm in longest axis); 9. Access site false aneurysm; 10. Units of red blood cells transfused after administration of Lava; 11. Duration of the index procedure, total and after administration of Lava; 12. Contrast administered during index procedure; 13. Fluoroscopy time during index procedure; 14. Length of stay in the intensive care unit after the index procedure; 15. Length of hospitalization, total and after the index procedure.
Study Population	The study population will include subjects with active arterial bleeding from the peripheral vasculature, excluding those with bleeding from the vessels of the heart, intracranial vasculature, intra-dural bleeding in the spinal canal, and post-partum hemorrhage.
Inclusion Criteria	The prospective study participant must meet each of the following criteria to be eligible for inclusion in the study: 1. Age ≥18 years; 2. Active arterial bleeding in the peripheral vasculature, documented on a suitable imaging study; 3. Subject or subject's legally authorized representative is able and authorized to provide written informed consent for the procedure and the study; 4. Subject is willing and able to comply with the specified follow-up evaluation schedule; 5. Life expectancy >30 days; 6. No prior embolization in the target territory.
Exclusion Criteria:	The prospective study participant must not have any of the following exclusion criteria present at the time of eligibility assessment: 1. Pregnancy or breast feeding. A woman who, in the Investigator's opinion, is of child-bearing potential must have a negative pregnancy test within 7 days before the index procedure;

	2. Coexisting signs of peritonitis or other active infection; 3. Participation in an investigational study of a new drug, biologic or device that has not reached its primary endpoint at the time of study screening; 4. Uncorrectable coagulopathies such as thrombocytopenia <40,000/ μL, international normalization ratio (INR) >2.0; 5. Contraindication to angiography or catheterization, including untreatable allergy to iodinated contrast media; 6. Anatomic arterial unsuitability such that, in the Investigator's opinion, the delivery catheter cannot gain access to the selected position for safe and intended embolization; 7. Known allergy or other contraindication to any components of Lava LES including dimethyl sulfoxide (DMSO); 8. More than 4 Target Lesions will require embolization, in the Investigator's opinion after performance of diagnostic angiography or another suitable imaging study.
Performance Goal	A 72% literature-derived performance goal was established for the primary effectiveness endpoint of 30-day Clinical Success. An 82% literature-derived performance goal was established for the primary safety endpoint of freedom from 30-day major adverse events (defined as a composite of five events).
Study Hypothesis Testing	The proportion of Target Lesions with 30-day Clinical Success will be tested against the 72% performance goal using a one-sided exact confidence interval with a one-sided alpha level of 0.025. The proportion of patients experiencing freedom from 30-day major adverse events will be tested against the 82% performance goal using a one-sided exact confidence interval with a one-sided alpha level of 0.025.
Sample Size Calculation	The study is powered for the primary effectiveness endpoint of Clinical Success. Using the literature-derived performance goal of 72%, anticipating an observed success rate of 84%, and based upon a one-sided 97.5% exact binominal test with a significance level of 0.025, the required sample size to achieve a level of 80% power is 101 Target Lesions. Assuming a 10% attrition rate through 30 days, a total of 113 subjects will need to be enrolled. Similarly, for primary safety endpoint, based on a literature-derived performance goal of 82% and an anticipated observed success rate of 92%, using a sample size of 101 provides 80% power to detect a difference of 9.9% using a one-sided exact binomial test with a significance level of 0.025.
Analytical Sets	The regulatory submission will be based on an approximate sample size of 113 subjects. The safety endpoints will be assessed in the Intent-to-Treat dataset. The effectiveness endpoints will be assessed in the Completed Cases dataset.
Pre-Enrollment Testing	• Medical history

	• Physical examination with vital signs and directed peripheral vascular examination • Laboratory assessment • Diagnostic angiogram at time of the planned index procedure, performed prior to the point of enrollment in the study. Eligibility is, in part, based upon the angiographic findings.
Follow-Up Schedule	Subjects have required follow-up evaluations at the following time points: 1. Hospital discharge; 2. 30±7 days after the index procedure. This evaluation can be performed via telephone with a member of the investigational site's research staff or with an in-person visit with the Investigator.
Clinical Events Committee	An independent Clinical Events Committee (CEC) will review all primary safety endpoint events, unanticipated adverse device effects, and other important safety occurrences as specified in the CEC Charter.
Data Safety Monitoring Board	An independent Data Safety Monitoring Board (DSMB) will review safety data from the study at predetermined time points and as deemed necessary by the Sponsor or the DSMB Chair. The DSMB will make recommendations on protocol modifications and continuation of the study.
Study Principal Investigators	Bulent Arslan MD Mahmood Razavi MD

1 INTRODUCTION AND BACKGROUND

1.1 Embolotherapy for Peripheral Arterial Hemorrhage

Peripheral arterial hemorrhage is caused by a variety of conditions including intrinsic disease, trauma or iatrogenic causes. These bleeds are often emergently addressed by interventional radiologists using trans-arterial embolization. These therapies control life-threatening hemorrhage through endovascular, image-guided, catheter-based techniques, and are often performed first-line, obviating the need for surgery. The agents used to embolize the target vessels or organs, may be metallic, animal-derived, synthetic, polymeric, or a hybrid of some of these materials that can either completely block blood flow or form a framework for in situ thrombosis and potentially desired local inflammation.[1] The objective of trans-arterial embolization of hemorrhage is to stop the acute bleeding and to restore hemodynamic stability, without causing end organ ischemia that could lead to infarction or dysfunction. Methods and embolic agent selection are determined by physician familiarity, preference and factors such as the desired duration of the intended occlusion, the "level" of vessel embolization (i.e., tissue capillary level leading to intended infarction as might be desired for a neoplasm versus large vessel level preserving collateral pathways bypassing the occluded artery), the ability to reach the intended target vessel using catheter technology, its caliber, the existence of a collateral arterial network, and the patient's coagulation function status.[2,3]

There are a limited number of products approved for treatment of peripheral arterial hemorrhage, but a much wider range of products are routinely used, each with reported advantages and disadvantages. Products differ in their delivery mechanisms, safety profiles, and sizes of vessels that can be occluded. Devices that have been reported to be used for treatment of peripheral arterial hemorrhage include stainless steel or platinum coils with or without fibers, Nitinol plugs with or without polymeric fabric, gelatin sponge particles, irregular polymeric particles (polyvinyl alcohol or PVA), synthetic, gelatin based, or hydrogel microspheres, and liquid embolic agents including sclerosants, cyanoacrylates, and synthetic polymers.[2-5]

Large mechanical embolic devices such as embolization coils and plugs have been cleared by the Food and Drug Administration (FDA) for embolization in the peripheral vasculature, and thus are on-label when used for peripheral arterial hemorrhage. Other embolic agents are used off-label but have become standard of care.[6] Coils and plugs typically require a functional coagulation system in the patient to form thrombus to occlude the vessel. In critically ill patients, this coagulation system is frequently compromised. Other patients may be on chronic antiplatelet or anticoagulation medications for cardiac or vascular comorbidities. Even if thrombus forms, the innate thrombolytic system may dissolve the thrombus, leading to delayed recanalization. Use of coils and plugs too proximally in larger vessels may also promote the immediate and delayed formation of collateral pathways that may allow hemorrhage to persist or recur.

Products used for occlusion of mid-sized vessels include gelatin sponge, polymeric particles, and microspheres. Several different formulations of PVA particles and of synthetic or hybrid microspheres have received FDA clearance for treatment of "arterio-venous malformation and hyper-vascular tumors". In addition, several microspheres have received FDA clearance for the treatment of uterine fibroid and benign prostatic hypertrophy. Some microspheres and PVA particles may be unsuitable for embolization of peripheral hemorrhage because of their risk of end-organ ischemia and infarction (due to their microscopic size). Porcine gelatin sponges such as gel-foam have been contraindicated for intravascular use, but their usage after cutting them into particles or cubes has been widely reported for intravascular applications. One gelatin sponge cube product recently received FDA clearance for hyper-vascular tumors. The advantages of gelatin sponge include its biodegradability and thus temporary nature of occlusion; however, the biodegradation may be unpredictable. In addition, intraprocedural preparation of gelatin sponge particles by the treating physician may result in a very wide range of particle sizes, including substantial numbers of particles small enough to cause end-organ infarction.

Two commercially available liquid embolic agents, Onyx™ (Medtronic, Irvine, CA), and Trufill® nBCA glue (DePuy Synthes/ Johnson & Johnson, Raynham, MA) are indicated for pre-surgical resection of brain arterio-venous malformations. They have no peripheral vascular indication, though their importance, clinical utility, and use in peripheral arterial hemorrhage have been widely reported. [6] These liquid agents bring unique value because they cause complete, predictable, and permanent large and middle size vessel occlusion, free of the risk of incomplete occlusion due to coagulopathy and delayed recanalization, as occurs with coils and plugs. They can also be prepared and used in a fashion that enables penetration into smaller downstream arteries and arcades distal to those that can be reached with microcatheters (i.e., embolization of multiple branches can be achieved from a single catheterization location).

BlackSwan Vascular, Inc. has developed its Lava™ Liquid Embolic System (Lava LES) to treat active hemorrhage in the peripheral arterial system. For the purposes of framing the indications for use under consideration, peripheral arteries include all arteries except those in the intracranial and intradural spaces serving the central nervous system and those of the heart.

1.2 Applications for Embolic Agents

The safe and effective use of liquid embolic agents has been reported for many other applications including for venous and lymphatic embolization, however, the current study intends to focus on demonstrating its safe and effective use for peripheral arterial hemorrhages only. The most common examples of peripheral arterial hemorrhage are described below:

1.2.1 Gastrointestinal Hemorrhage

Hemorrhage in the GI tract is one of the most common peripheral arterial bleeds and accounts for an estimated 300,000 hospitalizations annually in the USA. [7] GI bleeds are classified into upper

gastrointestinal bleeds (UGIB) or lower gastrointestinal bleeds (LGIB) depending on the location of the bleed. LGIB is any form of gastrointestinal bleeding in the lower gastrointestinal tract, defined as bleeding originating distal to the ligament of Treitz. LGIB is a common reason for seeking emergent medical attention and carries a high mortality rate. LGIB accounts for about 20%-30% of all gastrointestinal bleeding and reflects different pathologies from upper gastrointestinal bleeding. Approximately 75% of lower gastrointestinal bleeding cases involve the colon, 20% involve the rectum or anus, and 3–5% involve the small intestine. LGIB encompasses a wide spectrum of symptoms and signs, ranging from minor hematochezia to massive hemorrhage with hypovolemic shock and hemodynamic collapse. LGIB may be acute or chronic or both. Acute or overt LGIB has been defined as bleeding that is of recent duration, originates beyond the ligament of Treitz, manifests at hematochezia, and may result in instability of vital signs, and anemia with or without need for blood transfusion. Etiologies of LGIB may include vascular, inflammatory, neoplastic, or traumatic causes, including diverticular disease, angiodysplasia, inflammatory bowel disease, hemorrhoids, and rectal ulcers.

In addition to the etiologies listed above for LGIB, UGIB originates from a point in the gastrointestinal tract proximal to the ligament of Treitz and may be caused by erosive or ulcerative disease such as peptic ulcer disease, which may be related to use of nonsteroidal anti-inflammatory drugs and/or infection by helicobacter pylori, variceal hemorrhage secondary to portal hypertension, Mallory-Weiss tears from vomiting, and Dieulafoy lesions. Patients with UGIB typically present with hematemesis of fresh blood or of coffee-ground consistency, or with melena. Approximately 30% of all UGIB is from venous sources rather than peripheral arterial sources. As with LGIB, the clinical course can be acute, chronic, or both, and bleeding may be overt or occult.

1.2.2 Arterial Hemorrhage Associated with Trauma

In addition to bleeding from organic, disease-related complications (i.e., ulcer or aneurysm rupture), major hemorrhage can also be due to iatrogenic causes or external trauma. Uncontrolled bleeding is a significant factor in mortality after trauma and contributes to more than 40% of trauma-related deaths[2] and is the leading cause of potentially preventable death.[5] Trauma-related bleeding can result from injury to the head, trunk, or limbs and can involve vascular injury to internal organs, musculoskeletal structures or to the arteries themselves. Trans-catheter embolization is a well-established and effective first-line method for controlling bleeding from traumatic injuries, particularly when not treatable by external compression and open surgical methods are either ineffective or present too high a risk. It is routinely offered as an initial treatment of vascular injury in both unstable patients with acute hemorrhage, as well as, in meta-stable, sub-acute patients in whom empiric occlusion of a bleeding source, such as a visceral aneurysm or pseudoaneurysm, is essential to prevent, recurrent bleeding.[5]

1.2.3 Traumatic Splenic Arterial Hemorrhage

Embolization is commonly used as a nonsurgical treatment after blunt splenic trauma. Embolization can be performed super-selectively to control an identified focal bleeding site or can be performed less selectively to reduce global organ perfusion pressure to allow natural coagulation and healing, especially when there are multiple sites of bleeding. Embolization allows preservation of the spleen and reduces the risk of delayed exacerbation of rupture. Embolization may also be performed to treat arterio-venous fistula (AVF) or pseudoaneurysm (PSA) secondary to trauma. Embolization is indicated if cross-sectional imaging, usually computed tomography (CT), demonstrates active hemorrhage, AVF or PSA, or grade splenic injury. [2,5] Embolization may also be used for splenic vascular injury from penetrating trauma. Numerous studies over the past five decades have reported on the safety and efficacy of embolization for splenic trauma, resulting in decreased mortality and length of hospital stay.[8]

1.2.4 Other Traumatic Visceral Arterial Hemorrhage

Hepatic arterial embolization is performed to treat injury to the hepatic artery due to abdominal trauma, both blunt and penetrating. Damage to any portion of the hepatic arterial tree may lead to subcapsular, intra-biliary, or intraperitoneal hemorrhage and may be life-threatening. Similarly, renal arterial embolization is performed for severe hemorrhage due to traumatic injuries, including spontaneous hemorrhages. Other viscera, including the adrenal glands, pancreas, bladder, and uterus, may also suffer vascular injuries best treated by embolization. Preservation of visceral function is often achieved without the necessity for open surgical intervention.

1.2.5 Traumatic Musculoskeletal Arterial Hemorrhage

Pelvic fractures from blunt trauma such as vehicular accidents continue to be a main indication for embolotherapy. Pelvic hemorrhage is typically identified on CT scan, may be difficult or impossible to control by orthopedic or abdominopelvic surgery, but is routinely addressed emergently in the management of acutely injured patients by embolization. Similarly, traumatic hemorrhage in the extremities, thorax, retroperitoneum, and peri-spinal regions may also be treated most quickly and minimally invasively by embolization.

1.2.6 Iatrogenic Arterial Hemorrhage

In addition to accidental trauma, medical treatments may cause uncontrolled iatrogenic hemorrhage. Pharmacologic manipulation of platelet function or the coagulation cascade may result in spontaneous hemorrhage in viscera or the musculoskeletal system, including the psoas or rectus muscles. Even more common, surgery and other invasive interventions may inadvertently injure vascular structures, causing acute or delayed hemorrhage. Invasive procedures such as partial nephrectomy, partial hepatectomy, pancreatectomy, gastrectomy, colectomy, prostatectomy, hysterectomy, spinal and musculoskeletal fixation, robotically assisted surgery, and even Caesarean section may result in life-threatening post-operative hemorrhage that may be prohibitively difficult

or morbid to address by conventional open surgical means. Even minimally invasive procedures, such as upper or lower gastrointestinal endoscopy, cholangiopancreatography, sphincterotomy, polypectomy, bronchoscopy, stone extractions from the biliary or urinary tracts, biopsies, bone marrow aspirations, and tissue ablations may result in major hemorrhage requiring embolization.

Over five decades of use suggest that transcatheter arterial embolization is a safe and effective treatment for hemorrhage from gastrointestinal or other peripheral arteries for a wide variety of etiologies. The results led to the adoption of embolotherapy as a standard of care. Today, embolization is a time-tested, proven, image guided approach to control of life-threatening hemorrhage, and modern catheter and imaging technology allow the practitioner to reach virtually any bleeding source. Regardless of the site of hemorrhage, the goals of any embolization procedure are to stop the hemorrhage as quickly as possible, to ensure that hemorrhage does not recur, and to minimize ischemic complications from non-target embolization to territories adjacent to the site of hemorrhage.

2 INVESTIGATIONAL DEVICE

2.1 Overview

The study device is the Lava Liquid Embolic System (Lava LES). The Lava Liquid Embolic System (LES) consists of the Lava LES Kit (**Figure 1**) and the Lava Mixing Kit (**Figure 2**). **Table 1** summarized the components of the Lava LES.

Table 1. Summary of Investigational Device and Components

Investigational Device	Components	Parts
Lava LES	Lava LES Kit	• Lava embolic agent (Lava)- 1 vial • DMSO- 1 vial • 1cc DMSO syringe (yellow piston)- 1 each • 1cc delivery syringe (white piston)- 6 each
	Lava Mixing Kit	• Mixing manifold – 1 each • DMSO mixing syringes- 2 each

LES- Liquid embolic system

The Lava LES Kit comprises a sterile, sealed, serum vial containing the Lava liquid embolic suspension (Lava), a sterile, sealed, serum vial containing dimethyl sulfoxide (DMSO), and a sterile, sealed pouch containing DMSO compatible syringes.

Lava is an injectable, non-adhesive liquid embolic agent comprised of ethylene vinyl alcohol (EVOH) copolymer dissolved in dimethyl sulfoxide (DMSO) and suspended micronized tantalum powder to provide contrast for visualization under fluoroscopy.

The Lava Mixing Kit comprises a sterile, sealed pouch containing a mixing manifold and two sterile, sealed pouches, each containing a single DMSO compatible mixing syringe.

2.2 Manufacturer

The Lava LES is manufactured by BlackSwan Vascular, Inc. The adjunctive devices, including guidewires, sheaths, guides, and catheters are not supplied by BlackSwan Vascular, Inc.; these will be chosen at the Investigator's discretion from currently marketed devices.

2.3 Model Numbers

The Lava LES Kit is available in two product formulations, Lava-18 (nominal viscosity of 18 cSt), and Lava-34 (nominal viscosity of 33 cSt). Lava-18 will travel more distally and penetrate deeper into the vasculature due to its lower viscosity compared to the Lava-34. **Table 1** summarized the model numbers and descriptions of Lava LES Kits.

There are 4 Stock Keeping Units (SKUs) for Lava. There are two SKUs with a viscosity of 33 centistokes, Lava-34, supplied in 2 ml and 6 ml vials. There are two SKUs with a viscosity of 18 centistokes, Lava-18, each supplied in 2 ml and 6 ml vials.

Table 2. Model Numbers and Descriptions of Lava LES Kits

SKU	Model Name	Lava Volume (ml)	Lava Viscosity (centistokes, cSt)
[redacted]	Lava-34	6	33
[redacted]	Lava-34	2	33
[redacted]	Lava-18	6	18
[redacted]	Lava-18	2	18

The Lava Mixing Kit is available in 2 options; 2 ml and 6 ml. **Table 3** summarized the model numbers and descriptions of Lava Mixing Kits.

Table 3. Model Numbers and Descriptions of Lava Mixing Kits

SKU	Model Name	Volume (ml)
[redacted]	Lava Mixing Kit - 6 ml	6

[redacted]	Lava Mixing Kit - 2 ml	2

2.4 Device Traceability

Lot number will be used to trace devices in the study.

2.5 Indication for Use

The proposed indication for use is for embolization of arterial hemorrhage in the peripheral vasculature.

2.6 Device Description

The Lava LES consists of the Lava LES Kit and the Lava Mixing Kit.

The Lava LES Kit comprises the following system components contained in a product shelf carton:

- A sterile, sealed, serum vial containing Lava
- A sterile, sealed, serum vial containing DMSO
- A sterile, sealed pouch containing DMSO compatible syringes

Lava is an injectable, non-adhesive liquid embolic agent comprised of three ingredients; tantalum, DMSO, and EVOH. The EVOH copolymer dissolved in DMSO and suspended micronized tantalum powder to provide contrast for visualization under fluoroscopy. Lava is first prepared with the Lava Mixing Kit and then delivered to the target anatomy via a DMSO compatible microcatheter. The Lava precipitates into a spongy, coherent mass or cast upon exposure to blood at the targeted location. The DMSO compatible microcatheter is not part of the study device.

The Lava Mixing Kit is used for homogenization of the Lava and is available in two sizes to accommodate the different volumes of the Lava LES Kit. The Lava LES Mixing Kit comprises the following components contained in a product shelf carton:

- A sterile, sealed pouch containing a mixing manifold
- Two sterile, sealed pouches, each containing a single DMSO compatible mixing syringe

The 6 ml and 2 ml configurations of the Lava LES Kit are depicted in **Figure 1**. The mixing manifold component of the Lava Mixing Kit is depicted in **Figure 2**.

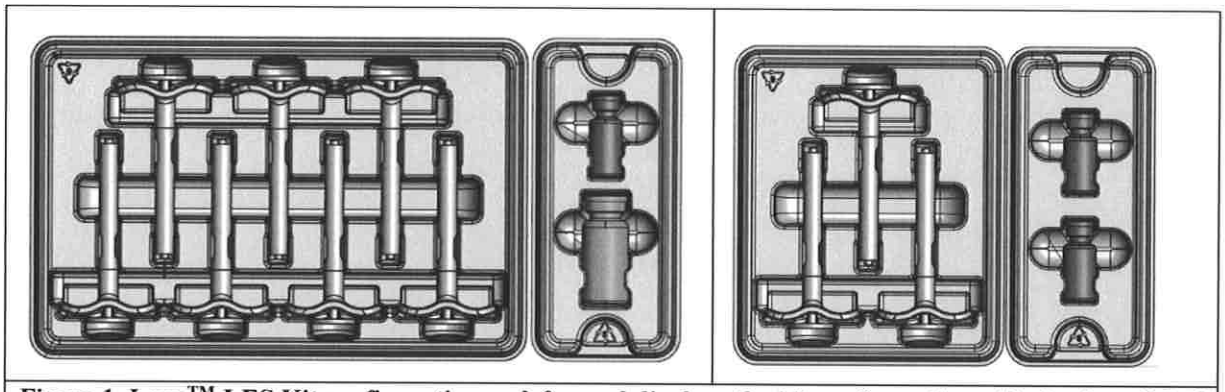

Figure 1. Lava™ LES Kit configurations: left panel displays the kit configuration with the 6 cc vial of Lava and right panel displays the kit configuration with the 2 cc vial of Lava

2.7 Method of Use

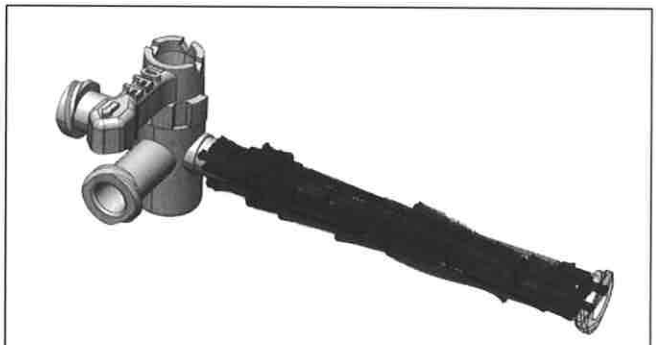

Figure 2. Mixing Manifold component from Lava Mixing Kit.

- The liquid embolic suspension is delivered to the patient through a DMSO compatible microcatheter. The catheter is selectively placed into the target vascular location and primed with DMSO prior to injecting the liquid embolic suspension. The liquid embolic suspension is delivered by controlled injection into the desired vascular location under fluoroscopic visualization. The total volume of liquid embolic suspension injected should not exceed 3.5 mL. The precipitation of the liquid embolic begins immediately upon exiting the distal end of the microcatheter, beginning from the outside of the embolus and proceeding to the center of embolus. Total precipitation occurs within minutes of exposure to blood or other aqueous media. The distance that the embolus travels prior to full precipitation is dependent on several factors, including the injection rate, the flow rate in the target vasculature, and the viscosity of the embolic.

3 PRIOR INVESTIGATIONS

While there are many investigations of other embolic agents, devices, and techniques, and while Onyx has been the subject of single center publications, there have been no prior investigations of Lava LES, to date.

4 STUDY OBJECTIVE

The objective of this study is to evaluate the safety and effectiveness of Lava LES embolotherapy for the treatment of hemorrhage from peripheral arteries.

Safety will be evaluated by assessing freedom from 30-day MAE, a composite endpoint that includes those complications that occur at the site of catheter insertion, along the pathway for access to the target arteries, and at the site of administration in the target territory or those non-target arterial beds where embolic agent was inadvertently administered. The MAE rate will be compared to the rates reported in the literature after treatment with other modalities currently used to treat peripheral artery hemorrhage.

Effectiveness will be evaluated by assessing the absence of bleeding in the treated target lesion after embolization with the Lava LES, without the need for reintervention through 30 days after the index procedure.

5 OUTCOME VARIABLES

5.1 Primary Safety Endpoint Definition

The primary safety endpoint is a composite of freedom from 30-day Major Adverse Events (MAEs). MAEs include the following events as adjudicated by an independent Clinical Events Committee (CEC);

1. Ischemia or infarction of the target territory;
2. Non-target embolization;
3. Allergic reactions to Lava;
4. Catheter breakage;
5. Catheter entrapment.

Each MAE element is determined after enrollment; any events that occur prior to the point of enrollment as defined in **Section 6.5**, below, are not included in the primary safety endpoint. The target territory or territories are specified by the Investigator at the time of enrollment; embolization to a non-target territory is defined as unintentional administration of Lava to a vascular bed outside of a target territory. Catheter breakage refers to defects in the luminal continuity of the microcatheter used to deliver Lava, but not to other catheters that may be used in other aspects of the procedure separate from the administration of Lava. Catheter kinks without defects in luminal continuity will not trigger the endpoint. Catheter entrapment, defined as the inability to withdraw the catheter refers to the catheter with which Lava is administered and is defined by the need for endovascular or open surgical procedures to remove the catheter or portions thereof. Retained portions of the catheter trigger the endpoint, irrespective whether additional endovascular or open surgical procedures were performed.

5.2 Primary Effectiveness Endpoint Definition

The primary effectiveness endpoint[a] is Clinical Success, defined as absence of bleeding from the target lesion after embolization with the Lava LES, without the need for emergency surgery, re-embolization, or other target lesion reinterventions within 30 days of the index procedure. Absence of bleeding is defined as no BARC Type 3 or greater bleeding occurring after the index procedure, either persistent or recurrent. The ascertainment of persistent or recurrent BARC Type 3 or greater bleeding does not include bleeding that occurred prior to the conclusion of the index procedure.

The primary effectiveness endpoint will be adjudicated by the CEC, relying on information from the source documents and/or the core laboratory findings of absence of bleeding.[b] Effectiveness relates to the target lesion(s) as defined by the Investigator at the index procedure.

5.3 Secondary Endpoints

The following measures will be assessed as secondary endpoints of the study:

1. Technical Success, defined as absence of angiographic evidence of bleeding from the target lesion at the conclusion of the index procedure;
2. Successful delivery of Lava and intact retrieval of the microcatheter;
3. Assessment of each element of the primary safety endpoint (MAE) as an individual component;
4. Symptomatic ischemia in the target territory that does not require intervention;
5. All-cause mortality;
6. Bleeding-related mortality (attributable to bleeding in a target territory);
7. Open surgical conversion for persistent or recurrent bleeding;
8. Device-related serious adverse events;
9. Procedure-related serious adverse events;
10. Access site hematoma (>5cm in longest axis);[c]
11. Access site false aneurysm;
12. Units of red blood cells transfused after administration of Lava;

[a] The effectiveness endpoint is lesion-based and not subject-based. Failure of the effectiveness endpoint is triggered by events that are referable to the specific lesion and not to other events referable to another lesion in the same subject. For example, if a subject has two lesions where the first is treated successfully but the other rebleeds and requires emergency surgery, effectiveness would have been achieved in the first lesion but not in the second.
[b] Core laboratory-determined assessment of bleeding is used for the primary and secondary endpoints. If core laboratory images are unavailable or uninterpretable, the site-reported determinations will be used.
[c] As measured on a duplex ultrasound study, assessed by the Core Laboratory.

13. Duration index procedure, total and after administration of Lava;
14. Contrast administered during index procedure;
15. Fluoroscopy time during index procedure;
16. Length of stay in the intensive care unit after the index procedure;
17. Length of hospitalization, total and after the index procedure.

6 STUDY METHODOLOGY

This study is a single-arm trial with primary safety and effectiveness endpoints, designed to assess the outcome after Lava LES arterial embolotherapy of hemorrhage from peripheral arterial vessels.

6.1 Study Design

The study is a multicenter, prospective, single-arm trial of the Lava LES in patients with peripheral arterial bleeding in need of treatment. Subjects will be enrolled at up to 20 investigational sites in the United States with no more than 25 subjects enrolled at any single site.

6.2 Informed Consent

Written, study-specific informed consent will be obtained from each prospective study participant prior to treatment with the Lava LES. The prospective study participant will be counseled that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Subjects will be consented for 1 year to allow for the ability to collect additional data, if initial study results indicate a need for additional longer-term information. The Investigator will keep the original Informed Consent Form (ICF) and a copy will be given to the subject.

Written informed consent may be obtained from a patient's legally authorized representative (LAR) in emergency procedures where informed consent cannot be reasonably obtained from the patient for reasons of hemodynamic instability, medications, or other conditions that prevent comprehension and consideration of the benefits and risks of study participation.[d] Consent from a LAR will be guided by the institutional local policies, state law, and the relevant IRB.

6.3 Study Eligibility

Prospective study participants include those that meet the following inclusion and exclusion criteria:

[d] A legally authorized representative is defined in 21 CFR 50.3(l) as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research."

6.3.1 Inclusion Criteria

The prospective study participant must meet each of the following criteria to be eligible for inclusion in the study:

1. Age ≥18 years;
2. Active arterial bleeding in the peripheral vasculature (defined in **Section 6.4**, below), documented on a suitable imaging study;[e]
3. Subject or subject's LAR is able and authorized provide written informed consent for the procedure and the study;
4. Willing and able to comply with the specified follow-up evaluation schedule;
5. Life expectancy >30 days;
6. No prior embolization in the target territory.

6.3.2 Exclusion Criteria

The prospective study participant must not have any of the following exclusion criteria present at the time of eligibility assessment:

1. Pregnancy or breast feeding. A woman who, in the Investigator's opinion, is of child-bearing potential must have a negative pregnancy test within 7 days before the index procedure;
2. Coexisting signs of peritonitis or other active infection;
3. Participation in an investigational study of a new drug, biologic or device that has not reached its primary endpoint at the time of study screening;
4. Uncorrectable coagulopathies such as thrombocytopenia <40,000/ μL, international normalization ratio (INR) >2.0;
5. Contraindication to angiography or catheterization, including untreatable allergy to iodinated contrast media;
6. Anatomic arterial unsuitability such that, in the Investigator's opinion, the delivery catheter cannot gain access to the selected position for safe and intended embolization;

[e] The site of bleeding must be documented either angiographically at the time of the index procedure or, if no bleeding is observed on the diagnostic angiogram, with a suitable imaging study performed within 48 hours of the index procedure that, in the Investigator's opinion, adequately localized bleeding to a territory or territories suitable for embolization. Empiric embolization, defined as embolization in the absence of arteriographic localization of the bleeding vessel at the index procedure angiogram, will be allowed for bleeding from sites other than the lower gastrointestinal tract (small intestine, colon, and rectum).

7. Known allergy or other contraindication to any components of Lava including dimethyl sulfoxide (DMSO);
8. More than 4 Target Lesions will require embolization, in the Investigator's opinion after performance of diagnostic angiography or another suitable imaging study.[f]

6.4 Peripheral Arterial Hemorrhage

Subjects will be eligible for enrollment if bleeding is localized within the peripheral arteries, as defined by gastrointestinal hemorrhage (esophagus, stomach, duodenum, small and large intestine), arterial hemorrhage associated with trauma, visceral artery hemorrhage (including splenic, hepatic, adrenal, pancreas, prostate, bladder, and uterus), traumatic musculoskeletal artery hemorrhage, bronchial artery hemorrhage, or iatrogenic arterial hemorrhage.

Patients with hemorrhage from the vessels of the heart, the intracranial vessels, the vertebral or carotid arteries or branches thereof, vessels of the spinal cord, and those with postpartum gynecological hemorrhage will be ineligible for inclusion in the study.

6.5 Point of Enrollment

An eligible prospective study participant will meet all eligibility criteria and be considered enrolled when the informed consent form has been signed by the prospective study participant, or the participant's LAR, and after successful arterial access has been established to the Target Lesion.

Consented patients in whom an index procedure is performed but the Investigator decides at the time of the index procedure not to use the Lava LES will be considered screen fails.[g]

6.6 Study Populations

Consented patients will be evaluated as follows:

6.6.1 Screen Fails

Patients who are consented but who, for whatever reason, are not enrolled (e.g., they do not meet the eligibility criteria after diagnostic angiography) will be considered screen failures and will be not be followed further. The reason for excluding these subjects from enrollment will be documented in the Electronic Data Capture (EDC) system.

[f] If the Investigator believed at the time of diagnostic imaging that 4 or fewer lesions required embolization but, during the course of treatment it is in the subject's best interest to embolize more than 4 lesions, the additional lesions must be treated with non-study agents/devices. Any complications related to the additionally embolized lesions will be considered procedure-related but not device-related events. Rebleeding documented to be from the additionally embolized lesions will not trigger the primary effectiveness endpoint.

[g] Provocative angiography may be performed at the Investigator's discretion. Complications from provocative angiography are considered procedure-related but not device-related events.

6.6.2 Intention-to-Treat Population

The Intention-to-Treat (ITT) population will include all consented subjects in whom the Lava LES study device entered the vasculature (as defined in **Section 6.5**, above), irrespective of adherence with the entry criteria, treatment received, subsequent withdrawal, or deviation from the Protocol.

6.6.3 Completed Cases Population

The Completed Cases (CC) population will include all ITT subjects who complete 30-day follow-up. The CC population will also include ITT subjects who experience failure of the primary effectiveness endpoint prior to the beginning of the 30-day follow-up timepoint, irrespective of their length of follow-up.

7 STATISTICS AND DATA ANALYSIS

7.1 Statistical Methodology

The objective of the statistical design for this study is to evaluate the safety and effectiveness of the Lava LES, as assessed in comparison to literature-derived performance goals. The safety and effectiveness performance goals were determined from a literature review of publications on treatment of bleeding peripheral vessels. A total of 67 publications comprising 2102 patients were included in this review.

7.2 Primary Safety Endpoint

The primary safety endpoint is the 30-day rate of MAE, defined by the occurrence of any one of the following events between enrollment and 30 days after the index procedure:

1. Ischemia or infarction of the target territory;
2. Non-target embolization;
3. Allergic reactions to Lava;
4. Catheter breakage;
5. Catheter entrapment.

See **Section 5.1**, above, for a complete description of the elements of the primary safety endpoint.

7.3 Primary Effectiveness Endpoint

The primary effectiveness endpoint is Clinical Success, defined as absence of bleeding from a target lesion after embolization with the Lava LES, without the need for emergency surgery, re-embolization, or other target lesion reinterventions within 30 days of the index procedure. Absence of bleeding is defined as no BARC Type 3 or greater bleeding occurring after the index procedure, either

persistent or recurrent. The ascertainment of persistent or recurrent BARC Type 3 or greater bleeding does not include bleeding that occurred prior to the conclusion of the index procedure.

See **Section 5.2**, above, for a complete description of the primary effectiveness endpoint.

7.4 Study Success Criteria

The study will be deemed successful if both the primary effectiveness and primary safety hypotheses are met. For the primary effectiveness endpoint, the lower limit of the one-sided 97.5% confidence interval must be greater than 72%. For the primary safety endpoint, the lower limit of one-sided 97.5% confidence interval must be great than 82%.

7.5 Secondary Endpoints

The following secondary endpoints will be assessed in the study:

1. Assessment of each element of the primary safety endpoint (MAEs) as individual components;
2. Symptomatic ischemia in the target territory that does not require intervention;
3. All-cause mortality;
4. Bleeding-related mortality (attributable to bleeding in a target territory);
5. Open surgical conversion for persistent or recurrent bleeding;
6. Device-related serious adverse events;
7. Procedure-related serious adverse events;
8. Access site hematoma (>5cm in longest axis);
9. Access site false aneurysm;
10. Units of red blood cells transfused after administration of Lava;
11. Duration of the index procedure, total and after administration of Lava;
12. Contrast administered during index procedure;
13. Fluoroscopy time during index procedure;
14. Length of stay in the intensive care unit after the index procedure;
15. Length of hospitalization, total and after the index procedure.

7.6 Subject Level and Lesion Level Analyses

The ITT dataset will be used for all safety endpoints. Each safety-related endpoint will be assessed on a subject-level basis; expressed as the number of subjects experiencing at least one event divided by the number of subjects with evaluable observations.

The CC dataset will be used for all effectiveness endpoints. Categorical effectiveness endpoints will be expressed as the number of Target Lesions meeting the effectiveness criteria divided by the number Target Lesions with evaluable observations. Continuous effectiveness endpoints will be assessed with mean or median and standard deviation or range, as appropriate for the distribution of data. Certain

effectiveness endpoints will be assessed on a lesion-level basis; for example, the primary effectiveness endpoint of Clinical Success. Other effectiveness endpoints will be assessed at the subject level; for example, measures related to resource utilization including procedure duration, contrast volume administered, and fluoroscopy time.

7.7 Missing or Incomplete Data

Every effort will be made to minimize the amount of missing data. Recognizing the difficulty of avoiding some missing data, however, data imputation methods with sensitivity imputation analyses will be carried out. Safety endpoint analyses will include all subjects experiencing at least one component of the safety endpoint or with follow-up to the lower limit of the follow-up window for the 30-day time point (i.e., the denominator will be adjusted for missing data). Target Lesions with unavailable effectiveness data will be assumed to have missing data at random and will be imputed by random selection with replacement of data from Target Lesions with complete data. The robustness of the multiple imputation outcome will be tested with a tipping point analysis encompassing all possible imputation outcomes.

7.8 Derivation of the Safety and Effectiveness Performance Goals

A literature search identified 67 publications reporting outcome for 2102 patients treated with embolotherapy for peripheral arterial hemorrhage.[h] A variety of embolic agents were used in the publications. Results were tabulated for technical success, clinical success, 30-day mortality, rebleeding, and non-target territory ischemia. Weighted averages were calculated as the number of patients with a specific type of event, divided by the number of patients with evaluable observations for that event type.

7.8.1 Safety Performance Goal

The safety performance goal is based on the available data from the literature review, as well as the Society of Interventional Radiology (SIR) Quality Improvement Guidelines for Percutaneous Embolization document. [9] The SIR document estimated a 2.5% to 8.0% (average 4.0%) rate of symptomatic ischemia after embolotherapy, and a non-target territory embolization rate of approximately 2.5%. Assuming a 1% rate for each of the three other MAE elements (allergic reaction to embolic agent, catheter breakage, inability to withdraw the catheter), a composite rate of 10% was estimated for the 30-day MAE primary safety endpoint. Based on this, a safety success rate analysis was estimated in the range of 88%-92%. Using the sample size of 101 patients derived for the study hypothesis for primary effectiveness, one-sided 97.5% lower Wilson-score confidence limits were calculated based on safety success rates in the clinical study varying in the range of 88.1%-92.1% and are shown in Table 4 below. Assuming that the safety success rate is

[h] The literature review was performed by BlackSwan Vascular and was included in the preparatory materials for the Q-submission meeting on June 7, 2019 (Q181438/S002). See Attachment 1 for list of references.

90.1% and the sample size is 101, the lower 97.5% confidence limit is 82.7%. Based on this analysis, a prespecified performance goal for the above-mentioned safety endpoint was chosen to be 82%.

Table 4. Lower Confidence Limit for Varying Safety Success Rates

Sample Size	# of Successes	Safety Success Rate	Lower 97.5% Wilson-score Confidence Limit
101	93	92.1%	85.1 %
101	92	91.1%	83.9 %
101	91	90.1%	82.7 %
101	90	89.1%	81.5%
101	89	88.1%	80.4%

7.8.2 Effectiveness Performance Goal

The objective of Lava LES embolotherapy is to occlude feeding vessels to bleeding target lesions. Clinical Success, the primary effectiveness endpoint, averaged approximated 80% in the 51 publications that reported the endpoint (**Attachment 1**). This rate was consistent with the expected outcomes reported in the Society of Interventional Radiology document. [9] An 8% margin was used to assign a effectiveness performance goal of 72%.

7.9 Sample Size

The study is powered for the primary effectiveness endpoint of Clinical Success. Based upon a one-sided 97.5% exact binominal test using a significance level of 0.025, the literature-derived performance goal of 72%, and an anticipated observed success rate of 84%,[i] the required sample size to achieve a level of 80% power is 101 Target Lesions. Assuming a 10% attrition rate through 30 days, a total of 113 subjects will need to be enrolled. (**Table 5**).

[i] The anticipated Clinical Success rate of 84% was estimated after discussions with the Sponsor's scientific advisors.

Table 5. Sample Size – Primary Effectiveness Endpoint

Clinical Success	
Performance Goal	72%
Anticipated Clinical Success rate	84%
Significance level	.025
Statistical test	One-sided exact binomial test
Desired power level	80%
Required sample size (Target Lesions)	101
Target Lesions required, assuming 10% attrition through 30 days	113

Calculations for the required sample size for the anticipated success rate for Clinical Success, ranging from 80% to 85% appear in **Table 6**, below.

Table 6. Sample Size Estimates for Varying Rates of Anticipated Success with the Lava LES

One-sided Alpha	**Power**	**Clinical Success (H_0)**	**Anticipated Success (H_A)**	**Sample Size Estimate**	**Sample Size with 10% Attrition**
0.025	80%	72%	80%	227	253
0.025	80%	72%	81%	179	199
0.025	80%	72%	82%	142	158
0.025	80%	72%	83%	118	132
0.025	80%	72%	84%	101	113
0.025	80%	72%	85%	79	88

7.10 Study Hypotheses

Success or failure of the study will be based on the primary effectiveness and safety endpoints, with descriptive assessment of the primary and secondary safety endpoints. The primary effectiveness endpoint of Clinical Success will be assessed for all Target Lesions in the Completed Cases dataset and will be calculated on a per lesion basis.

H_0: $P_E \leq PG_E$, versus

H_A: $P_E > PG_E$

Where P_E is the proportion of Target Lesions with Clinical Success and PG_E is the effectiveness performance goal (**Section 7.8.2**).

The primary safety endpoint of freedom from major adverse events will be assessed for all subjects in the ITT population. The null and alternative statistical hypotheses for the primary safety endpoint will be defined as follows:

$$H0: Ps \leq PG_S \text{ versus } HA: Ps > PG_S,$$

where Ps is the population primary safety success rate in the Test group and PG_S is the safety performance goal.

The study will be considered a success if the primary effectiveness and primary safety endpoints meets their respective performance goals, translating into the observation of a one-sided 97.5% lower confidence limits of the point estimate above 72% and 82%, respectively.

7.11 Subgroup and Other Analyses

Subgroup analyses for primary effectiveness endpoint, clinical success rate, will be performed for sex, target territory (gastrointestinal and non-gastrointestinal), and for etiology (traumatic and non-traumatic). The subgroup analyses will be descriptive in nature and will not be powered for hypothesis testing. Statistical hypothesis testing will be conducted to assess the similarity of the primary effectiveness endpoint across each sub-group using a Fisher's exact test and a significance level of 0.15.

7.12 Changes to Planned Analyses

All analyses will be detailed in the Statistical Analysis Plan (SAP). Any changes to the planned analyses will be documented as amendments to the SAP and in the Clinical Study Report.

7.13 Interim Analyses

There will be no formal interim analyses in this study. The Data Safety Monitoring Board (DSMB) will review safety data with meetings prespecified in the DSMB Charter and as additionally determined by the Sponsor or the DSMB Chair. The DSMB will review the primary effectiveness

endpoint, since ineffective treatment contributes to the overall benefit-risk profile of subject exposure to the Lava LES.

7.14 Assessment of Poolability

Poolability of data across clinical study sites is justified based on clinical characteristics of the study design; all study sites use the same Protocol; sites are monitored for protocol compliance, and the data gathering instruments are identical. However, a statistical assessment of poolability will be performed by comparing the baseline characteristics across study sites. For categorical baseline variables such as sex, a generalized Fisher's exact test or equivalent test will be used and for quantitative variables, parametric or non-parametric analysis of variance (general linear models or an equivalent procedure) will be used.

The above statistical analyses do not result in an impediment to pooling, but rather assess the balance of baseline covariates across study sites. If any baseline covariate is found to be statistically significant by this process, multivariate analyses will be done to determine if the imbalance affected study outcome. This is done by using both the variable found out of balance and study site as possible covariates.

It may be necessary to combine two or more low enrolling study sites into pseudo-sites to allow these analyses. The justification for pooling all the data to estimate a common effect across study sites requires the homogeneity of response across study sites. A Fisher-Freeman-Halton test analyzing the rates of success for the primary effectiveness endpoint, clinical success rate, will be employed to test whether investigational sites differ with respect to primary effectiveness. The test of inhomogeneity of response will be based on a two-sided test using a 0.15 level of significance. Study sites with fewer than 6 subjects will be excluded for the analysis of poolability.

8 ASSESSMENTS AND FOLLOW-UP SCHEDULE

Study participants will be screened for study eligibility pre-procedure and final eligibility will be determined at the time of the diagnostic arteriogram at beginning of the index procedure. Enrollment will occur at the point at which the Investigator makes the decision to perform embolotherapy with the study device (Lava LES) in a previously consented patient. The follow-up period will comprise the post-procedure period through hospital discharge and the 30-day period following the index procedure. Assessments are summarized in the Schedule of Assessments (**Table 7**, below).

Table 7. Schedule of Assessments

Assessment	Screening/ Baseline	Index Procedure	Hospital Discharge	30 days ± 7 days*	Unscheduled Visits

Informed consent	<24 hours before the IP				
Medical history	<24 hours before the IP				
Verification elgibility criteria	<24 hours before the IP	X			
Pregnancy testing	<7 days before the IP				
Physical Examination†	<24 hours before the IP	X	X		X
Diagnostic Angiography		X	X‡		X‡
Embolic Therapy with Lava LES		X			
Adverse event assessment		X	X	X	X
Concomitant medications		X	X	X	X
Laboratory testing§	<24 hours before the IP		X		X

IP- Index procedure

** This assessment can be performed via telephone with a member of the investigational site's research staff or with an in-person visit with the Investigator.*

†Physical examination will include vital signs and an examination of the target territory (as appropriate; e.g. the subject's limb) pre-procedure. Physical examination will also include an examination of the access site and target territory at the conclusion of the index procedure and at in-person scheduled or unscheduled follow-up visits. Abnormalities of the vascular system will prompt a duplex ultrasound or another appropriate imaging study to exclude false aneurysm, hematoma, arteriovenous fistula, dissection, or deep venous thrombosis.

‡Diagnostic angiography is repeated after the index procedure for continued bleeding or rebleeding, at the Investigator's discretion. Laboratory

§The following laboratory tests are required to be reported: the lowest hemoglobin reported during the current bleeding episode, the last hemoglobin, platelet count, and international normalized ratio (INR) prior to the index procedure, and the hemoglobin, platelet count and INR at discharge and at any unscheduled visits.

8.1 Screening/ Baseline Assessment

Prospective study participants will undergo a baseline, pre-procedure history and physical exam as part of the standard-of-care for these patients. Females deemed by the Investigator to be of reproductive potential must have a negative pregnancy test performed within 7 days of the index procedure. The final disposition (e.g. enrollment, ineligibility, or decision by subject or physician not to enroll) must be noted. Review of the inclusion/ exclusion criteria will be performed to ensure subject meets criteria. If the subject meets all inclusion criteria and does not meet any exclusion criteria, the subject may be invited to participate in the study and informed consent will take place prior to the procedure.

The following procedures will be performed at the Screening visit prior to the procedure. All data must be recorded in the subject's case report form (CRF):

- Demographic information (detailed in **Section 8.1.1**)

- Physical examination with vital signs and directed peripheral vascular examination
- Baseline Characteristics (detailed in **Section 8.1.2**)
- Laboratory assessment (detailed in **Section 8.1.3**)
- Diagnostic angiogram at time of the planned index procedure, performed prior to the point of enrollment in the study; eligibility is, in part, based on the anatomic findings of the angiogram

8.1.1 Demographics

Demographic variables measured at enrollment will include age, sex, race, ethnicity, body weight, height, and calculated basal metabolic index.

8.1.2 Baseline Characteristics

Baseline characteristics will refer to those characteristics present before the index procedure and will include medical comorbidities, selected baseline medications (anticoagulants, antiplatelets), etiology of bleeding (traumatic, iatrogenic, congenital vascular lesion, Mallory-Weiss tear, ulcer, benign neoplasm, malignant neoplasm, unknown, other), location of the target territory (upper gastrointestinal, lower gastrointestinal, non-intestinal visceral, extremity, pulmonary), bleeding vessel(s), duration of bleeding, lowest recorded systolic blood pressure after onset of bleeding, lowest hemoglobin after onset of bleeding, units of red blood cells transfused after onset of bleeding and prior to the index procedure, last platelet count and international normalized ratio prior to the index procedure.

8.1.3 Laboratory Assessments

Clinical laboratory tests are expected to be performed at this visit to establish baseline levels (i.e. hemoglobin, platelet counts, and INR) to evaluate for lowest hemoglobin after onset of bleeding, and the last hemoglobin, platelet count, and INR prior to the index procedure. The panel of tests standardly performed at the institution for patients with similar conditions related to peripheral bleeding will be performed at the Investigator's discretion. It is recognized that specific panels may vary between institutions. Laboratory data will not be specially analyzed but will be used only to support adverse event evaluations.

8.2 Treatment Assessment

Diagnostic angiography will be performed to confirm bleeding prior to the index procedure. The index procedure begins with the start of arterial access and ends when the dressing is applied to the access site. The index procedure is performed under fluoroscopic guidance with administration of contrast as necessary. The Investigator may elect to use provocative methods to identify the site of bleeding and adjunctive embolic agents and devices at their discretion. When utilized, such methods and devices

will be recorded on the procedure electronic case report form (eCRF).[j] The "treatment phase" begins at the point of administration of Lava.

8.3 Target Lesions, Vessels, and Territories

The Target Lesion is specified by the Investigator at the index procedure, after diagnostic angiography but prior to embolization, and is defined as a hemorrhage site planned for embolization with the Lava LES. Up to 4 Target Lesions may be treated in a subject.

Target Vessels are arteries where the tip of the delivery catheter is located at the time Lava administration is planned.[k] More than one Target Vessel may supply a single Target Lesion. Each Target Lesion is linked to a Target Territory, where the Target Territory is defined as the vascular territory supplied by a Target Vessel, within a single organ, extremity, or tissue bed.[l]

Non-Target Embolization is defined when Lava is unintentionally administered to a vascular bed outside a Target Territory. Non-target territory is defined as the vascular territory outside of the planned Target Territory specified by the Investigator prior to embolization at that site. Inadvertent embolization of Lava to a Non-Target Territory is an element of the composite MAE endpoint.

8.4 Hospital Discharge Assessment

Subjects will be assessed prior to but not more than 48 hours before hospital discharge. A physical examination will be performed. In addition, examination of the access site will be performed, along with an examination of the lower extremity vasculature. Clinical laboratory tests are expected to be performed at this visit to evaluate for lowest hemoglobin after onset of bleeding, last platelet count, and INR. Selected baseline medications (anticoagulants, antiplatelets) will be recorded. Adverse events and any rebleeding episodes or reinterventions will be recorded, as well as units of red blood cells transfused and measures of resource utility such as length of ICU stay and hospital length of stay. An arterial duplex ultrasound examination will be required for abnormalities at the access site (hematoma, mass, diminished peripheral pulses, thrill or bruit) and a venous duplex study will be performed for leg edema or other signs suggestive of deep venous thrombosis or venous injury.

If a subject has not been discharged by the 23rd post-procedure day, the discharge visit may be omitted without protocol deviation; supplanted by the 30-day visit.

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[j] The use of adjunctive embolic devices such as coils or occluders is considered part and parcel of current embolotherapy technique. The use of such devices will not otherwise constitute effectiveness failure of the Lava LES study device. Complications related to the use of adjunctive devices will be considered procedure-related but not device-related events.

[k] Target Vessels are specified at the time the Investigator is about to begin administration of Lava. Should the catheter be inadvertently displaced during administration, the Target Vessel remains that vessel that the Investigator specified as the planned location of the catheter tip for embolization.

[l] As an example, for a bleeding duodenal ulcer fed by the gastroduodenal artery and where the Investigator gained access to the gastroduodenal artery, the Target Lesion is the ulcer in the first part of the duodenum, the Target Vessel is the gastroduodenal artery, and the Target Territory is the first part of the duodenum.

8.5 Follow-Up Assessment

A 30-day follow-up visit will be performed; with a visit window between 23 and 37 days. The visit may be done via telephone. Any abnormalities will prompt an in-person visit.[m] Selected baseline medications (anticoagulants, antiplatelets) will be recorded. Adverse events will be recorded, as will any red blood cell transfusions between discharge and the 30 days. An arterial duplex ultrasound examination will be required for abnormalities at the access site (hematoma, mass, diminished peripheral pulses, thrill or bruit) and a venous duplex study will be performed for leg edema or other signs suggestive of deep venous thrombosis or venous injury.

8.6 Unscheduled Post Treatment Follow-Up Visits

Unscheduled visits are defined as unplanned visits prompted by recurrent bleeding or a site-reported device- or procedure-related complication. Unrelated visits do not need to be reported as unscheduled visits, but any adverse event, related or unrelated, must be reported on the adverse event eCRF. Subjects who have unscheduled follow-up visits will undergo the same assessments as for the hospital discharge and the unscheduled visit eCRF will contain the same information as the hospital discharge eCRF, with the addition of the reason for the visit.

If an unscheduled visit occurs within the window for the 30-day visit, both the unscheduled visit eCRF and the 30-day visit eCRF must be completed.

When the unscheduled visit is performed for rebleeding, clinical laboratory tests will include the lowest hemoglobin level after discharge, the last hemoglobin level, platelet count, and INR. Selected baseline medications (anticoagulants, antiplatelets) will be recorded. Physical examination and examination of access sites and lower extremity vasculature will be performed. An arterial duplex ultrasound examination will be required for abnormalities at the access site (hematoma, mass, diminished peripheral pulses, thrill or bruit) and a venous duplex study will be performed for leg edema or other signs suggestive of deep venous thrombosis or venous injury. Diagnostic angiography is repeated for continued bleeding or rebleeding at the Investigator's discretion.

8.7 Reinterventions

Reinterventions are defined as those secondary procedures, endovascular or open surgical, that occur after the subject has left the angiography suite after the index procedure and are performed as a result of residual bleeding, recurrent bleeding, or a device- or procedure-related events. Procedures unrelated to bleeding or to complications from the device or the procedure are not reported as reinterventions but may be reported as unrelated adverse events (see **Section 10.1**, below).

8.8 Withdrawals and Loss to Follow-Up

[m] If an in-window telephone visit prompts an in-person visit that, for scheduling reasons, cannot not performed within the 30-day window, no protocol deviation will be reported. Any abnormalities detected at a late 30-day in-person visit will be assigned to the 30-day visit timepoint.

Study participation is completely voluntary, and each subject is free to withdraw from the study at any time. An investigator also has the right to withdraw the subject from the study in the event of reasons concerning the health or well-being of the subject, or in the case of lack of cooperation. Should a subject decide to withdraw for any reason, or should the investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete, final evaluation at the time of the subject's withdrawal must be made and an explanation given as to why the subject is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal must be recorded on the subject's End of Study eCRF. If the reason for the withdrawal is a device- or procedure-related AE, the event must be reported to the Sponsor and recorded on the eCRF.

If the procedure is aborted, the subject does not need to complete the follow-up assessments, unless the subject is converted to surgical repair. The subject's enrollment roster position will not be made available to other subjects.

If a subject dies during the course of the study, the Sponsor will request an autopsy provided the subject authorized an autopsy in the event of death during the course of the study. Autopsy observations should include documentation of condition of body organs and determination of device and/or procedure relationship to death.

All efforts will be made to retain subjects in order to collect data at the 30-day the follow-up visit. Due diligence in reaching the subject must be made by:

- Two documented telephone contact attempts, emails, or regular postal mail letters; and
- A certified letter

After the above attempts were made, if no response is obtained, the final evaluation of a given subject will be the last visit at which study-related procedures were performed on that subject. The End of Study eCRF page will need to be completed and communication attempts must be documented.

9 STUDY MANAGEMENT CONSIDERATIONS

9.1 Data Management

The Sponsor and/or assigned designee will be responsible for the quality control of the data. Data will be retained for at least 2 years after the termination/completion of the study or after the approval/withdrawal of the marketing application, whichever occurs later. All other source data, source documents, eCRFs, copies of Protocols and protocol amendments, device accountability forms, correspondence, subject identification lists, informed consent forms, and other essential documents must also be retained for a period of at least 2 years as detailed above. The Sponsor will inform the investigator/institution when these documents are no longer required to be retained.

No study document or image will be destroyed without prior written agreement from the Sponsor. Should the Investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to the Sponsor.

9.2 Core Laboratory

An independent core laboratory will be used for the assessment of angiographic endpoints. All protocol-specified imaging studies will be sent to the Core Laboratory for evaluation. Angiographic bleeding absence will be assessed by the Core Laboratory and will supersede the site-determined findings where differences exist. The Core Laboratory interpretations will comprise the primary measures for reporting the primary endpoints and will be used by the CEC as the imaging endpoints for the adjudication of events. The Core Laboratory Imaging Manual will specify details including the image transfer process and imaging endpoint assessment.

9.3 Modifications to the Clinical Investigational Plan

No changes from the final approved signed Clinical Investigational Plan (Protocol) will be initiated without the Institutional Review Board's (IRB's) prior written approval of the amendment, except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration. The Principal Investigator will acknowledge the amendment by signing the new version of the Protocol.

9.4 Protocol Deviations

A protocol deviation is the non-adherence to or divergence from the protocol-specific study procedures. For example, deviations from the inclusion and exclusion criteria, deviations from the schedule of required follow-up assessments, improper or lack of consent, and lack of IRB approval, would all be considered protocol deviations.

Subject eligibility for the study is determined by site-measured anatomic criteria; not by core laboratory values. However, enrollment of subjects with core laboratory-determined anatomic measurements on the baseline, pre-interventional angiogram will not be protocol deviations.

9.4.1 Planned Protocol Deviations

Non-urgent, planned protocol deviations require prior written approval by the Sponsor and, if the deviation affects the affect the scientific soundness of the plan or the rights, safety, or welfare of subjects, prior approval from the IRB and FDA is necessary. A protocol deviation undertaken to protect the life or physical well-being of the patient in an emergency is a special circumstance that needs no prior approval but which must be reported to the Sponsor and the reviewing IRB within 5 working days. The Sponsor must report the deviation to the FDA within 5 working days after the Sponsor learns of the deviation.[n] No other type of prospective protocol deviation is permitted without prior approval.

9.4.2 Major and Minor Protocol Deviations

While the FDA does not define major versus minor protocol deviations, the following guidelines will be used in this study. Major deviations will include though divergences from the Protocol that a) affect the rights, safety, and welfare of a study participant, or b) compromise data integrity. Protocol deviations that involve the inclusion or exclusion criteria will be considered major deviations, as will failure to collect primary endpoint data (e.g. as might occur with a missed critical follow-up visit). Out-of-window visits will be considered minor protocol deviations, as will missed non-critical assessments (e.g. laboratory tests not crucial to the primary endpoints or to the subject's safety), and failure to use the proper version of the informed consent form.

9.4.3 Responsibility for Reporting Protocol Deviations

The Investigator is responsible for the reporting of protocol deviations on the subject's protocol deviation eCRF. When an unreported protocol deviation is identified by the Sponsor or designee through monitoring or other means, the Sponsor or designee will query the Investigator for entry of the deviation. When there remains disagreement between the Investigator and the Sponsor regarding a protocol deviation, the deviation can be considered at a special meeting of the CEC. In this case, the findings of the CEC will prevail.

A record of all protocol deviations will be maintained and reviewed throughout the conduct of the study. The Sponsor will address major or recurrent deviations at a site and take appropriate corresponding action. Continued non-compliance with the Protocol may lead to termination of the Investigator's or the investigational site's participation in the study.

9.5 Information to Study Personnel

The Investigator is responsible for providing study information to all research staff members involved in the study or in any element of subject management, both before starting the study procedures and during the course of the study (e.g., when new staff become involved). The Investigator must ensure

[n] Procedures for reporting deviations from the investigational plan are outlined in 21 CFR 812.150.

that all study staff members are qualified by education, experience, and training to perform their specific responsibilities.

The Sponsor representative and/or designee, e.g. a representative of its Contract Research Organization (CRO), is responsible for explaining the Protocol to all study staff, including the Investigator, and for assessing their compliance with the Protocol throughout the study. Additional information may be made available during the study when new staff become involved in the study, and as otherwise agreed upon with the Investigator.

10 ASSESSMENT OF SAFETY

10.1 Defining Adverse Events

An adverse event is an untoward medical occurrence or exacerbation of an existing medical condition subsequent to the experimental therapy. Adverse events are categorized in several ways:

Severity

- **Mild**: No limitation of usual activities, no therapy or only symptomatic therapy required to treat the injury or illness.
- **Moderate**: Some limitation of usual activities or specific therapy is required.
- **Severe**: Inability to carry out usual activities, hospitalization, emergency treatment, life threatening events, or death.

Anticipated versus Unanticipated

- Anticipated
- Unanticipated

Relatedness

- Device-related
- Procedure-related

The relationship to the device or to the procedure is classified by the following levels of certainty:

- **Unrelated**: The clinical event is completely independent of study procedure/study device and/or evidence exists that the event is definitely related to another etiology.
- **Possibly related**: The clinical event occurs within a reasonable time sequence to study procedure/study device and there is some evidence to "possibly" suggest a causal relationship. However, the influence of other factors such as underlying disease, concomitant medications, or concurrent treatment may have contributed to the event.

- **Definitely related**: The clinical event occurs in a plausible time relationship to study procedure/study device and cannot be explained by any concurrent disease or other devices, drugs or chemicals.
- **Relationship unknown**: The relationship to the study procedure/study device is not known.

Seriousness

Adverse events will be categorized as either serious or non-serious. A Serious Adverse Event (SAE) is an event that meets at least one of the following:

- Is fatal
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Results in permanent impairment of a body function or permanent damage to a body structure
- Results in hospitalization or prolongs a hospitalization
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

Major Adverse Event (MAE)

MAEs comprise a subcategory of adverse events defined for this clinical study. MAEs include any of the primary safety endpoint components, as defined in **Section 5.1**, above.

Unanticipated Adverse Device Effect (UADE)

An 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 application), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects." **Section 15.1** (below) includes a list of possible adverse events associated with the study device and the index procedure, including those events considered major device-related events and major morbidity. UADE are reportable at all time points throughout the trial and require submission to the Sponsor. The Investigator must report UADEs to the Sponsor within 2 business days of learning of the event.[o]

10.2 Reporting of Adverse Events

[o] The 2-day timeframe refers to 2 business days from the point at which the Investigator makes the determination that the event is a UADE. This timepoint may be after the point at which the Investigator learns of the event itself.

All adverse events, non-serious and serious, that occur during the study must be reported on the Adverse Event eCRF. The report should include, wherever possible, time of onset, severity, duration, outcome, and the Investigator's medical judgment as to the relationship of the adverse event to the study device, procedure, (i.e. not related, possibly related, definitely related, or relationship unknown).[p]

All SAEs must be reported to the Sponsor or its CRO within 5 business days of the Investigator's knowledge of the event. The event is reported in the electronic data capture system. IRB notification of the adverse event may also be required, depending on the conditions of approval or requirements of the respective committee. Any UADEs must be reported to the Sponsor/CRO within 1 working day from when the Investigator first learns of it.

Non-serious reportable adverse events are to be submitted via the EDC in a timely fashion. Certain reportable events may require adjudication; therefore, supporting documentation must be sent to the Sponsor/CRO upon request.

Events that occur before consenting of the patient are not reported. Adverse events that occur after consenting in patients that are screen fails, in other words, in those for whom the Investigator decides not to treat with the study device (Lava LES) will also not be reported. Adverse events that occur after consenting of the patient in enrolled subjects (i.e. those for whom the Investigator decided to treat with the study device) will not be reported if they occur prior to the start of the index procedure (defined as the beginning of arterial access; see **Section 6.5**, above), but will be reported as procedure-related adverse events if they occur after the start of the index procedure but before Lava is administered into the delivery catheter.

Events related to preexisting conditions are not reported unless there is worsening of the condition after enrollment (or after the start of the index procedure, as specified in the paragraph above).

Reinterventions are not reported as adverse events; rather, the event that prompted the reintervention (for example, rebleeding) is reported as the adverse event and the reintervention is reported as an outcome of that event.

10.3 Independent Medical Monitor

The independent Medical Monitor will be a board certified or board eligible licensed physician independent from the Sponsor. The Medical Monitor will be trained to the Protocol, a Safety Plan (if one is utilized) and the CEC Charter. The Medical Monitor will review every adverse event and device deficiency in the study. Adverse events will be classified as to seriousness, relatedness, whether they

[p] Each adverse event will be reviewed by the independent Medical Monitor for seriousness, relatedness, and whether it is anticipated. Certain events, as specified in the CEC Charter, will also undergo adjudication by the CEC. If the Investigator and the Medical Monitor disagree on an element of an adverse event, the Medical Monitor's classification will prevail for endpoint reporting purposes. If the CEC classification differs from that of either the Investigator or the Medical Monitor, the CEC classification will prevail.

are anticipated, and whether they meet a trigger for CEC adjudication, as specified in the CEC Charter. The Medical Monitor will re-review adverse events where new information has been reported. The Medical Monitor will determine whether re-adjudication is necessary, based upon new information.

10.4 Clinical Events Committee

The CEC will be comprised of independent physicians who are not participants in the study. The CEC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study which are based on the Protocol. All members of the CEC will be blinded to the primary results of the trial. The CEC will review and adjudicate appropriate clinical events on a regular basis. The events requiring adjudication will include those related to the device and to the primary safety and effectiveness endpoints, guided by a CEC charter.

10.5 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will be responsible to ensuring that the study is being conducted ethically and to adjudicate all possibly and definitely device- and/or procedure-related serious adverse events. The DSMB membership is represented from the key medical disciplines involved with the study procedure and may include an external biostatistician. None of the members may be directly involved with the clinical trial. The Sponsor has contracted a Clinical Research Organization to organize, facilitate, and document meetings for the DSMB for this trial. The DSMB will meet regularly and as necessary, guided by the DSMB Charter.

11 DEVICE ACCOUNTIBILITY

11.1 Accountability and Procedures

1. Each device shipment must be documented on the Device Accountability Log and include the receipt, dispensing, and return of investigational devices.
2. When a shipment is received, the Investigator (or designee) must record on the Device Accountability Log the date received and the Catalog and Lot Number of each device. It is recommended that the Packing List also be signed and dated.
3. Investigational devices must be kept in a secure, limited access storage area under recommended storage conditions (room temperature).
4. During the study, the following information must also be noted on the Device Accountability Log:
    - Identification number of the subject for whom the device was intended
    - Procedure date

5. The Device Accountability Log must be readily available for inspection by representatives from the Sponsor, the IRB, and/or other relevant regulatory authorities at any time.
6. The Device Accountability Log and device storage locations will be reviewed during monitoring visits.
7. All unused investigational devices must be returned to the Sponsor once it is determined they will not be used. Upon completion of the study, all unused investigational devices must be returned to the Sponsor if any remain at the site. The monitor must verify return at the close out visit, or before.

12 STUDY ADMINISTRATION

12.1 Site Initiation

A Site Initiation Visit (SIV) will be conducted by the Sponsor or other appropriate designee, for example, its CRO, to ensure that all study supplies are present, to ensure proper training of the Investigator and study staff members in study-specific procedures, to ensure regulatory requirements are fulfilled prior to enrollment of the first study subject at a site, and to verify the site facilities and equipment are appropriate for conduct of the study.

The following items will be reviewed at the SIV. All training will be documented and must contain signatures of participants:

1. Introduction and overview of agenda;
2. Obligations of the Investigator, including his/her responsibilities to ensure only appropriately qualified staff participate in the study conduct, and notification to the Sponsor or its CRO of any change in staff listed on the Delegation of Authority (refer to the site's Regulatory Binder) during the course of the study;
3. Protocol (overall review including, but not limited to, inclusion/exclusion criteria, recruitment/withdrawal of subjects, study restrictions);
4. Completion and maintenance of the Delegation of Authority;
5. Adverse experience reporting and unanticipated adverse device effect (UADE) reporting;
6. eCRFs (procedures, corrections, timely completion, retention);
7. Source document preparation and retention;
8. Role of the IRB;
9. Informed Consent process;

10. Study file documents and document retention (ensure all pertinent regulatory documents are collected prior to the site starting the study);
11. Clinical supplies and device management (storage and accountability; device dispensing, labeling, and packaging);
12. Clinical laboratory facilities;
13. Requirements for reporting any clinical data back to the Sponsor. (e.g., annual and final reports);
14. Monitoring schedule/plan;
15. Other items that should be discussed: background and purpose of the study, previous studies/data, regulatory requirements, policy for publishing trial results, any special equipment required.

12.2 Clinical Site Monitoring

Interim monitoring will be conducted by the Sponsor or designees (e.g. CRO) to ensure compliance with standard operating procedures (SOPs), the Protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary liaison between the Sponsor and the Investigator. The main responsibilities of the monitor are to visit the Investigator before, during, and after the study to ensure adherence to the Protocol; to verify all data are correctly and completely recorded and reported; and confirm that informed consent is obtained and recorded for each subject before study participation.

The study monitor will contact and visit the Investigator at regular intervals throughout the study, as guided by the study Monitoring Plan. The monitor will be allowed to check and verify the various records (eCRFs and other pertinent source data records) relating to the study to verify adherence to the Protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

As part of the supervision of the study progress, other Sponsor personnel may accompany the study monitor on visits to the study center. The Investigator and research staff must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of monitoring visits.

12.3 Study Termination

The Sponsor and applicable regulatory authorities have the right to terminate the entire study or an investigational site at any time. The DSMB may recommend study termination to the Sponsor, but the Sponsor holds the ultimate responsibility and authority for termination in this regard. If the Sponsor chooses not to follow the DSMB's recommendation for study termination, the circumstance underlying this decision must be reported to the IRBs and the FDA.

Situations that could warrant study termination include, but are not limited to:

1. Increased incidence of adverse experiences and/or the severity of such, suggestive of a potential, device-related health hazard;
2. Insufficient subject enrollment;
3. Recurrent protocol non-compliance, violations or deviations;
4. Inaccurate, incomplete, and/or untimely data recording, on a recurrent basis;
5. Lack of cooperation with monitoring visits (e.g., failure to adequately prepare for visits, address action items from one visit to the next, or provide access to medical records).

12.4 Data Handling and Recordkeeping

12.4.1 Completing, Signing and Archiving Case Report Forms

The Investigator must keep a separate subject identification list showing enrollment numbers, names, and dates of birth to allow unambiguous identification of each subject included in the study. It is recommended a note be made in the medical record that the subject is participating in a clinical research study.

The required data will be recorded on the eCRFs. A web-based EDC will be used to record and manage study data. eCRF completion guidelines, the instructions for electronic data entry, will be developed in conjunction with the Sponsor, the CRO, and/or the EDC vendor. The eCRFs will be completed electronically, with reasons documented for missing data. All eCRFs must be kept in good order and updated so they always reflect the latest observations on the subjects participating in the study.

The Investigator will sign the appropriate screens of the eCRF and source documentation. eCRF corrections will be made electronically and signed electronically by the Investigator. An embedded audit trail will capture the date, time and user making updates and changes to the electronic data.

Because it is important to have proper data collection in a timely manner, within 2 business days, the Investigator/Study Coordinator shall complete the eCRFs and provide them to the monitor upon request. When the monitor requests additional data or clarification of data for the eCRF, the request must be answered satisfactorily before the next monitoring visit.

12.4.2 Data Management and Archiving

The Sponsor will be responsible for the processing and quality control of the data. Source data for safety will be retained for at least 2 years after the termination/completion of the study or after the approval/withdrawal of the marketing application, whichever occurs later. All other source data, eCRFs, copies of Protocols and protocol amendments, device accountability forms, correspondence, subject identification lists, informed consent forms, and other essential documents must be retained for a period of at least 2 years after the last approval of the marketing application and until there are

no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational device. The Sponsor will inform the Investigator/ Institution when these documents are no longer required to be retained.

No study document or image will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to the Sponsor.

12.4.3 Direct Access to Source Data

The Sponsor, auditors, and health authority inspectors (or their agents) will be given direct access to source data and documentation (e.g., medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements.

The Investigator must maintain the primary records, (i.e., source documents) of each subject's data. Examples of source documents are hospital records, office visit records, examining physician's findings or progress notes, consultant's written opinion or notes, laboratory reports, device inventory, device label records, and eCRFs that are used as the source.

The Investigator will maintain a confidential subject identification list that allows the unambiguous identification of each subject with cross-referencing of the unique subject identifier and the subject's name and other identifying information (e.g. date of birth). The confidential subject identification list will be retained at the site. All study-related documents must be retained by the investigational site until notification by the Sponsor.

13 ETHICS

13.1 Informed Consent

Written informed consent must be obtained for each subject before any study-specific procedures or assessments are done and, specifically, prior to the subject being treated with the Lava LES. Written informed consent will be obtained after the aims, methods, anticipated benefits, and potential hazards are explained.

If required by institutional policy, informed consent will be obtained prior to review of Baseline and Screening data. A Screening Consent Form may also be available to secure permission from the subject for reviewing prospective subject information (if requested/required by site or IRB policy) prior to the subject agreeing to participate in the trial and signing the study-specific Informed Consent Form.

The subject's or their Legally Authorized Representamen's willingness to participate in the study will be documented in writing in a study-specific Informed Consent Form, which will be signed and dated by the subject or their Legally Authorized Representative and a witness.[q] The Investigator will keep the original consent form and a copy will be given to the subject. It will be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Subjects will be consented for 3 years to allow for the ability to collect additional data, if initial study results indicate a need for additional long-term information (i.e., during the post-approval phase).

13.2 Institutional Review Board

This study must be approved by an appropriate IRB at each investigational site. Securing the approval is the responsibility of the Investigator, as defined by ISO 14155-1 and FDA regulations (21 CFR Part 56) prior to starting the study. The Sponsor must receive a copy of the IRB approval letter (or equivalent documentation) for the Protocol and Informed Consent Form before the study can be started at that site or devices shipped to that Investigator.

The IRB and Sponsor must approve any significant changes to the Protocol as well as a change of Principal Investigator. Documentation of the IRB approval must be provided to the Sponsor. Records of all study review and approval documents must be maintained by the Investigator in the Regulatory Binder and are subject to inspection by the Sponsor or regulatory authority during or after completion of the study. Serious Adverse Events and deaths must also be reported to the IRB and Sponsor (reference **Section 10** for reporting instructions).

The Investigator must notify the IRB, as per their reporting guidelines, and the Sponsor when he or she deviates from the Protocol. The Sponsor must be notified of all relevant action taken by the IRB and must receive a copy of all study-related correspondence between the Investigator and the IRB.

The IRB must receive notification of the completion of the study and final report within 3 months of study completion or termination. A copy of these reports must be provided to the Sponsor. The Investigator must maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents submitted.

13.3 Confidentiality Regarding Study Subjects

The Investigator must ensure that the privacy of all subjects, including their personal identity and all personal medical information, will always be maintained. Subjects will not be identified by their names, but by an individual identification code (i.e., initials and identification number) in eCRFs and other documents or images transferred to the Sponsor.

[q] Prospective study participants may be unable to provide adequate consent due to medications or the systemic effects of the hemorrhage. In such cases, consent may be obtained from a Legally Authorized Representative, provided this is allowed by the relevant IRB.

Personal health information (PHI) may be reviewed for the purpose of verifying data recorded in the eCRFs. The monitor may conduct source document verification on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. PHI will always be treated as confidential.

13.4 Participating Institutions and Investigators

Study sites and Investigators will be selected based on a variety of factors including, but not limited to, experience with endovascular techniques, access to required facilities and equipment, sufficient and adequately trained personnel, and availability of potential subjects. The criteria used for determination will be documented. No other centers/institutions are intended to participate in this study without permission from the relevant regulatory authority.

13.5 Agreements

All Principal Investigators and their Sub-Investigators or Co-Investigators must sign an Investigator Agreement. BlackSwan Inc. (or the authorized CRO) must receive a copy of the signed Investigator Agreements before the study may be started at that institution or devices shipped. Any Investigators joining the study after the site has been initiated may not receive devices or participate until an agreement is signed and received by the Sponsor.

13.6 Responsibilities

Investigator responsibilities include, but are not limited to, the following:

1. Conducting the study in accordance with this investigational plan, signed agreement, and applicable regulations protecting the rights and safety of study subjects;
2. Informing all subjects that the device being utilized is for investigational purposes only, and ensuring that the requirements relating to obtaining informed consent and IRB approval are met;
3. Ensuring that informed consent is obtained for each study subject in accordance with applicable regulations (e.g., ISO 14155-1, 21 CFR Part 50);
4. Ensuring that IRB approval is secured prior to starting the study and ensuring continuing review and approval as required throughout the investigation;
5. Ensuring all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations, are adequately qualified and trained, and meet their commitments;
6. Maintaining adequate and accurate records and ensuring those records are available for inspection at any time;
7. Ensuring that conducting the study does not give rise to conflict of interest (financial disclosure is required);

8. Controlling of all investigational devices under investigation.

14 DATA SECURITY AND SCIENTIFIC INTEGRITY

14.1 Access to Data

The Sponsor, auditors, and health authority inspectors (or their agents) will be given access to source data and documentation (e.g., medical charts/records, laboratory test results, printouts, videotapes, etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements.

The Investigator must always maintain the primary records (source documentations) of each subject's data. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, device inventory, device label records, and eCRFs that are used as the source.

The Investigator will maintain a confidential subject identification list that allows the unambiguous identification of each subject. All study-related documents must be kept until notification by BlackSwan Vascular Inc.

14.2 Security and Confidentiality

The Investigator must ensure that the privacy of all subjects, including their personal identity and all personal medical information, will always be maintained. In eCRFs and other documents or image material submitted to the Sponsor, subjects will not be identified by their names, but by an identification code (i.e., subject number).

Personal medical information may be reviewed for the purpose of verifying data recorded in the eCRFs. The monitor may perform source data verification on behalf of the Sponsor or regulatory authorities. Personal medical information will always be treated as confidential.

15 RISK BENEFIT ANALYSIS

15.1 Risks to the Subjects

Treatment with the Lava LES is may pose significant risks to the subject, although these risks are not expected to be greater than with the current standard of care for treatment of bleeding peripheral vessels. A summary of some of the known risks are identified in **Table 8**, below; however, there may be risks that are not known or are unforeseen at this time. The risks include those related to the device and to the procedure, including those related to concomitant medications used periprocedurally and during follow-up.

There are other health risks and discomforts associated with the testing that patients will undergo before and after their procedure, including, but not limited to, bruising during blood collection, pain and bruising at the access site and radiation exposure during imaging procedures.

Table 8. Known risks of peripheral artery embolotherapy

Event Category	Event
Vascular	Vessel perforation
	False aneurysm
	Arterial dissection
	Mural thrombus formation
	Vessel occlusion, thrombotic or otherwise
	Arteriovenous fistula
	Distal atheroembolism
	Inadvertent embolization of a non-target vessel or territory
Access site	Infection
	Pain at site
	Serous drainage
	Lymphorrhea
	Hematoma
	Ecchymosis
Cardiac	Myocardial infarction
	Congestive heart failure
	Arrhythmia
	Valve disorders; stenosis and insufficiency
	Hypertension
	Hypotension
Venous	Deep venous thrombosis
	Pulmonary embolism

Table 8. Known risks of peripheral artery embolotherapy

Event Category	Event
	Paradoxical embolization
Local	Leg edema
	Leg pain
	Back pain
Cerebrovascular	Transient ischemic attack
	Stroke
	Intracranial hemorrhage
Genitourinary	Urinary retention
	Urinary tract infection
	Renal stones
	Renal insufficiency, failure
	Hematuria
	Impotence and other disorders of sexual function
Pulmonary	Exacerbation of chronic lung disease
	Pneumonia
	Respiratory failure
	Bronchitis
	Bronchospasm
Gastrointestinal	Peptic ulcer disease
	Reflux esophagitis
	Nausea and vomiting
	Diarrhea
	Constipation
	Hepatitis
	Hepatic insufficiency

Table 8. Known risks of peripheral artery embolotherapy

Event Category	Event
	Cholelithiasis / cholecystitis
Metabolic/systemic disorders	Electrolyte imbalances
	Hyperglycemia
	Hypoglycemia
	Fluid overload
	Dehydration
	Thrombocytopenia
	Leukopenia
	Anemia with or without need for transfusion
	Myoglobinemia, myoglobinuria
Device-related	Embolization of device components
	Loss of device components within vascular tree
	Inability to extract device from vascular tree
	Allergic reactions to device components
	Allergic reactions to concomitant medications
Miscellaneous	Sepsis
	Psychiatric disorders including depression
	Mental status changes
	Insomnia

15.2 Risk Mitigation

The Sponsor designed the Lava LES and the Protocol to minimize risks to the study participants. Study eligibility criteria were formulated to limit use of the study device to subjects and Target Lesions that fit the device specifications. Evaluation of safety data by an independent CEC and DSMB and assessment of imaging studies by an independent core laboratory will provide an ongoing assessment of safety-related events, both individually and in aggregate.

15.3 Benefit to Subjects

It is hoped that the Lava LES will provide additional treatment options for percutaneous treatment of subjects with hemorrhage from peripheral vessels. The avoidance of an open surgical procedure is advantageous in these often very ill patients.

15.4 Study Justification

This study is justified considering previous work showing benefit obtained using embolotherapy for bleeding from peripheral vessels. Despite reports of widespread use and acceptance, to date, the use of marketed liquid embolic agents has not been approved for use in the peripheral vessels the United States. This study will attempt to build on past results with other agents and devices and, potentially, identify additional benefits of liquid embolic agent Lava for the treatment of bleeding peripheral vessels. The objective evaluation of the study device will be assured through the performance of a clinical trial that uses a standardized protocol, pre-specified endpoints and statistical testing, an adequate sample size in appropriate study population, independent CEC and DSMB committees, and an independent core laboratory, and clinical site monitoring of original source documents.

16 ELECTRONIC DATA COLLECTION

An EDC will be used in this study for recording data. Where entries in the EDC are not based upon the subject's medical record, worksheets can be utilized but each must be signed and dated by the site's Principal Investigator. The medical record and the signed and dated worksheets will comprise the original source documentation. Where discrepancies exist between the medical record and worksheets, information in the medical record will prevail.

Source documents will be verified for alignment with EDC fields. There will be 100% source document verification in this trial; all EDC fields will be checked against information in the source documents.

17 ABBREVIATIONS

The following abbreviations are used in this document:

Abbreviation	Description
AVF	Arteriovenous fistula
CC	Completed cases
CEC	Clinical events committee
CRO	Contract research organization
cSt	Centistoke
DMSO	Dimethyl sulfoxide
DSMB	Data and safety monitoring board
eCRF	Electronic case report form
EDC	Electronic data collection
FDA	Food and Drug Administration
ICF	Informed consent form
ICU	Intensive care unit
INR	International normalization ratio
IRB	Institutional review board
ITT	Intent to treat
LAR	Legally authorized representative
LES	Liquid Embolic System
LGIB	Lower gastrointestinal bleed
MAE	Major adverse event
PHI	Personal Health Information
PSA	Pseudoaneurysm
PVA	Polyvinyl alcohol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIR	Society of Interventional Radiology

SIV	Site initiation visit
SOP	Standard Operating Procedures
UADE	Unanticipated adverse device effect
UGIB	Upper gastrointestinal bleed

18 DEFINITIONS

Category	Term	Definition
BARC Bleeding	Types 0 – 2 (do not trigger endpoint)	Type 0: no bleeding Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation.
	Types 3 – 5 (endpoint trigger)	Type 3: Clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below: Type 3a: • Overt bleeding plus hemoglobin drop of ≥3 to <5 g/dL* (provided hemoglobin drop is related to bleed) • Overt bleeding plus hemoglobin drop 3to5 g/dL, (provided hemoglobin drop is related to bleeding). Hemoglobin drop should be corrected for intracurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase hemoglobin by 1 g/dL. Type 3b: • Overt bleeding plus hemoglobin drop ≥5 g/dL, provided hemoglobin drop is related to bleed). Hemoglobin drop should be corrected for intracurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase hemoglobin by 1 g/dL. • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)

Category	Term	Definition
		• Bleeding requiring intravenous vasoactive drugs Type 3c: • Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal); subcategories confirmed by autopsy, imaging, or lumbar puncture • Intraocular bleed compromising vision Type 4: Coronary artery bypass-related bleeding; not applicable. Type 5: Fatal bleeding is bleeding that directly causes death with no other explainable cause. The site of fatal bleeding is specified as intracranial gastrointestinal, retroperitoneal, pulmonary, pericardial, genitourinary, or other. BARC fatal bleeding is categorized as either definite or probable as follows: Type 5a: Probable fatal bleeding (type 5a) is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging. Type 5b: Definite fatal bleeding (type 5b) is bleeding that is directly observed (by either clinical specimen such as blood, emesis, stool or imaging) or confirmed on autopsy.
Clinical Success		Absence of bleeding in a Target Lesion after embolization with the Lava LES and any adjunctive devices employed during the index procedure, without the need for emergency surgery, re-embolization, or other target territory reinterventions within 30 days of the index procedure.
Device-Related Events		Device-related events constitute those events that are deemed directly attributable to the Lava LES itself. Catheter entrapment will be considered a device-related adverse event, as will rebleeding after the index procedure. Continued bleeding, i.e. failure of the Lava LES to arrest hemorrhage, will constitute failure of the effectiveness endpoint but is not an adverse event, in and of itself. An event that is related to a prior device-related event is also considered to be device-related.
Hemorrhage	Bleeding	Bleeding is defined with respect to the Investigator-assigned

Category	Term	Definition
		target territories. Bleeding outside of a target territory is not tabulated in the primary or secondary endpoints, except for access site bleeding which is not tabulated in the primary endpoint but is included in the secondary access-site endpoints.
	Absence of Bleeding	No visible bleeding by angiography performed during the index procedure, assessed by the core laboratory unless images are unavailable or unevaluable, in which case the site-reported determination will be used.
	Recurrent Bleeding	CEC-adjudicated bleeding in a target territory defined at the time of a core-laboratory assessed post-index procedure angiogram or BARC Type 3a or greater bleeding irrespective of angiographic findings.
	Persistent Bleeding	Bleeding that persists at the final angiogram performed at the index procedure, assessed by the core laboratory unless images are unavailable or unevaluable, in which case the site-reported determination will be used.
	Lower Gastrointestinal Bleeding	Defined as bleeding that originates beyond the ligament of Treitz.
	Upper Gastrointestinal Bleeding	Defined as bleeding that originates below the ligament of Treitz.
Index Procedure		Defined as the start of arterial access and ends when the subject leaves the angiography suite. Access to the target territory and administration of Lava is considered the treatment phase.
Major Adverse Events		For the purposes of this study and the primary safety endpoint, Major Adverse Events (MAE) include any of the following, as adjudicated by the Clinical Events Committee: 1. Ischemia or infarction of the target territory; 2. Non-target embolization; 3. Allergic reactions to Lava; 4. Catheter breakage; 5. Catheter entrapment.
	Ischemia or infarction of the target territory	Reduction in blood flow to the target territory after the index procedure that results in the need for endovascular or open surgical intervention, or results in the death of the subject irrespective of whether an intervention was performed.
	Non-target embolization	Inadvertent embolization of Lava to a vascular territory that was not specified as the target territory by the Investigator,

Category	Term	Definition
		documented angiographically, at an open surgical reintervention, on surgical pathology, or at autopsy.
	Allergic reaction to Lava	Documented hypersensitivity reaction to Lava, characterized by urticaria, bronchospasm, hypotension, facial edema, and/or other signs and symptoms of allergy, as adjudicated by the CEC as related to Lava.
	Catheter breakage	Breakage of the catheter used to deliver Lava, resulting in a luminal catheter defect at the portion of the catheter that resided within the subject's vasculature. Kinks are not considered breakage. Breaks of other catheters, sheaths, and guides do not trigger this component of the composite MAE endpoint.
	Catheter entrapment	Inability to extract the catheter used for Lava delivery, due to adherence to the Lava material, requiring endovascular or open surgical intervention to remove the catheter or retained pieces of the catheter. The endpoint is triggered if pieces of the catheter are retained in the subject's vasculature at the conclusion of the index procedure.
Non-Target Territory		A vascular territory outside of the planned Target Territory specified by the Investigator prior to embolization at that site. Inadvertent embolization of Lava to a Non-Target Territory is an element of the composite MAE endpoint.
Procedure-Related		A procedure-related event is an event that occurs during the index procedure or within 30 days of the index procedure-irrespective of causation but not otherwise classified as a device-related event (i.e. an event that is device-related need not also be reported as procedure-related). As well, procedure-related adverse events include any events related to a remedial procedure necessary to treat the target territory (e.g. a rebleeding episode). An event related to a prior procedure-related event is also considered to be procedure-related.
Reintervention		Defined as those secondary procedures, endovascular or open surgical, that occur after the subject has left the angiography suite after the index procedure and are performed as a result of residual bleeding, recurrent bleeding, or a device- or procedure-related events.
Serious Adverse Event		An adverse event where the outcome is one of the following: 1. Death; 2. Life-threatening, where the patient was at substantial

Category	Term	Definition
		risk of dying or continued use of the product might have resulted in death; 3. Hospitalization or prolongation of an existing hospitalization; 4. Disability or permanent damage, interfering with the patient's ability to conduct normal life functions; 5. Congenital anomaly or birth defect; 6. Required intervention to prevent permanent impairment.
Target Lesion		A hemorrhage site planned for embolization with the Lava LES, as specified by the Investigator at the index procedure after diagnostic angiography but prior to embolization of that area. Up to 4 Target Lesions may be treated in a subject.
Target Territory		The vascular territory supplied by a Target Vessel, within a single organ, extremity, or tissue bed
Target Vessel		A vessel in which the tip of the delivery catheter is located at the time Lava administration is begun. More than one Target Vessel may supply a Target Lesion.
Technical Success		Absence of angiographic evidence of bleeding in the Target Lesion at the conclusion of the index procedure.
Unanticipated Adverse Device Effect		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.
Unscheduled Visits		Unplanned visits prompted by recurrent bleeding or a site-reported device- or procedure-related complication.

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SIGNATURE APPROVAL PAGE

Liquid Embolization of Arterial Hemorrhages in Peripheral Vasculature

The LAVA Study

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Signed: _____ Date: _____

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Signed: _____ Date: _____

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LAVA PROTOCOL AGREEMENT

Pivotal Investigational Device Exemption Trial for the Lava™ Liquid Embolic System.

Investigator Name	Title
Site Name	Site Number

I have read the Protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined therein.

I will provide copies of the Protocol and all information on the device relating to past non-clinical and clinical experience, which were furnished to me by BlackSwan Vascular, Inc., the Sponsor, to all physicians and other study personnel responsible to me who participate in this study, and will discuss this material with them to ensure that they are fully informed regarding the device and the conduct of the study.

I agree to keep records on all subject information (e.g., source documents and informed consent forms), device shipments and return forms, and all other information collected during the study, in accordance with local and national regulations.

Investigator Signature	**Date**

ATTACHMENTS

ATTACHMENT 1- Performance Goal List of Literature References

1. Abdulmalak G, Chevallier O, Falvo N, et al. Safety and efficacy of transcatheter embolization with Glubran((R))2 cyanoacrylate glue for acute arterial bleeding: a single-center experience with 104 patients. Abdominal radiology (New York). 2018;43(3):723-733.

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