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BlackSwan Vascular, Inc.
A Sirtex company

LAVA™

Instructions for Use (IFU)

LAVA® Liquid Embolic System

CAUTION

U.S. federal law restricts the sale, distribution, and use of this product to physicians or as prescribed by a physician.

This device should be used only by physicians with a thorough understanding of angiography and percutaneous interventional procedures.

DESCRIPTION

The LAVA Liquid Embolic System (LES) consists of the LAVA LES Kit and the LAVA Mixing Kit.

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 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.

LAVA is delivered through a DMSO compatible delivery microcatheter.

The LAVA LES Kit is available in two product formulations, LAVA-18 (nominal viscosity of 20 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. Both product formulations precipitate into a spongy, coherent mass or cast upon exposure to blood at the targeted location.

PRINCIPLE OF OPERATION

LAVA is delivered by slow controlled injection through a microcatheter into the target peripheral vasculature under fluoroscopic control. The DMSO dissipates into the blood, causing the EVOH copolymer to precipitate while the tantalum remains suspended in situ to form a spongy, coherent embolus. LAVA immediately forms a skin as the polymeric embolus solidifies from the outside to the inside, while traveling more in the lesion. Since LAVA is non-adhesive, the microcatheter can be left in place while slow, controlled injections are performed. Post embolization angiography can be conducted with the delivery microcatheter in place, enabling the physician to make additional injections through the same microcatheter, if necessary.

INDICATIONS FOR USE

LAVA LES is indicated for embolization of arterial hemorrhage in the peripheral vasculature.

HOW SUPPLIED

The LAVA LES product family consists of four (4) sterile LAVA LES kits and two (2) sterile LAVA Mixing Kits, with each kit supplied separately as follows:

1. **LAVA-18, 2 mL** (2 mL volume), DMSO (2 mL volume), two 1 mL delivery syringes, one 1 mL DMSO syringe;
2. **LAVA-18, 6 mL** (6 mL volume), DMSO (2 mL volume), six 1 mL delivery syringes, one 1 mL DMSO syringe;
3. **LAVA-34, 2 mL** (2 mL volume), DMSO (2 mL volume), two 1 mL delivery syringes, one 1 mL DMSO syringe;
4. **LAVA-34, 6 mL** (6 mL volume), DMSO (2 mL volume), six 1 mL delivery syringes, one 1 mL DMSO syringe;
5. **LAVA Mixing Kit** – 2 mL (two 3 mL mixing syringes, one mixing manifold) to be used with the LAVA-18, 2 mL product and the LAVA-34, 2 mL product;
6. **LAVA Mixing Kit** – 6 mL (two 6 mL mixing syringes, one mixing manifold) to be used with the LAVA-18, 6 mL product and the LAVA-34, 6 mL product.

CONTRAINDICATIONS

LAVA LES is not indicated for use in pregnant women, neonates or individuals with significant liver or kidney function impairment. Safety for these patient groups has not been evaluated.

POTENTIAL COMPLICATIONS

Potential adverse effects (e.g., complications) associated with the use of the device include:

- Non-target embolization
- Ischemia or infarction of the target territory
- Allergic reactions to device components
- Catheter breakage
- Catheter entrapment
- Inadvertent embolization of a non-target vessel or territory
- Embolization of device components
- Access site hematoma or ecchymosis
- Access site false aneurysm
- Pain at access site
- Arterial dissection
- Mural thrombus formation
- Vessel perforation
- Hemorrhage
- Recanalization
- Vessel perforation
- Arteriovenous fistula
- Distal atheroembolism
- Infection
- Sepsis
- Serous drainage
- Lymphorrhea
- Leg edema
- Leg pain
- Back pain

For the specific adverse events that occurred in the clinical study, please see CLINICAL STUDY RESULTS below.

WARNINGS

- DO NOT use monopolar electrocautery devices for surgical resection of tissue embolized with LAVA due to a possibility of electrical arcing with tantalum metal in the embolic cast. Bipolar devices should be used with caution.
- Use only DMSO compatible microcatheters. LAVA LES has been tested for compatibility with Terumo Medical Progreat®, Boston Scientific Renegade®, and Merit Medical Maestro® microcatheters. Also, use only the DMSO compatible syringes supplied with the LAVA LES Kit. Use of non DMSO compatible microcatheters and syringes may result in degradation that can potentially result in unexpected complications such as thromboembolic events.
- The LAVA LES should be used only by physicians with peripheral vascular training and a thorough knowledge of the pathology to be treated, angiographic techniques, and super-selective embolization. Performing embolization to occlude blood vessels in the peripheral vasculature is a high-risk procedure.
- If the vessel wall is compromised, LAVA could escape outside the vascular space. It may result in a subacute inflammatory response to the material and tissue damage.
- Dimethyl sulfoxide (DMSO) can initiate the liberation of histamine that may result in an occasional hypersensitivity reaction. If anaphylactoid symptoms develop, appropriate therapy should be instituted.
- DO NOT perform a therapeutic embolization when high blood flow precludes safe injection of LAVA.
- Special attention must be taken to the positioning of the microcatheter tip. The microcatheter tip should be placed to minimize the potential of embolization of non- target vessels or tissues.
- Mix LAVA per the “LAVA Mixing and Preparation” section of this IFU and inject LAVA immediately after mixing. Failure to prepare and mix LAVA per the “LAVA Mixing and Preparation” section of this IFU may result in inadequate suspension of the tantalum, resulting in inadequate fluoroscopic visualization during delivery. If LAVA injection is delayed, tantalum settling can occur within the syringe resulting in poor visualization during injection.

- Adequate fluoroscopic visualization must be maintained during LAVA delivery or non-target vessel embolization may result. If visualization is lost at any time during the embolization procedure, halt LAVA delivery until adequate visualization is re- established.
- Premature solidification of LAVA may occur if the microcatheter luer contacts any amount of saline, blood, or contrast.
- The recommended injection rate for each LAVA LES Kit product configuration is as follows:

LAVA LES Kit		**Recommended Microcatheter ID**	**Recommended Injection Rate**
Product	SKU		
LAVA-18, 2 mL	SLLES182	≥ 0.021 inch	≤ 0.3 mL/ min
LAVA-18, 6 mL	SLLES186		
LAVA-34, 2 mL	SLLES342		
LAVA-34, 6 mL	SLLES346		

- DO NOT exceed an injection rate of 0.3 mL/min of DMSO or LAVA into the vasculature as this may result in vasospasm and/or angionecrosis.
- DO NOT use palm of hand to advance plunger during injection of DMSO or LAVA as this may result in microcatheter rupture due to over pressurization in the event of microcatheter occlusion.
- DO NOT allow more than 1 cm of LAVA to reflux back over the microcatheter tip. Angioarchitecture, vasospasm, excessive LAVA reflux, or prolonged injection time may result in difficult microcatheter removal and potential entrapment. Excessive force to remove an entrapped microcatheter may cause serious hemorrhage. The long-term effects of an entrapped microcatheter that is left in a patient are unknown, but potentially could include clot formation, infection, or microcatheter migration.
- DO NOT attempt to clear a microcatheter or inject any material through it after use with LAVA. Such attempts may lead to embolization of unintended areas.
- DO NOT interrupt LAVA injection for longer than two minutes prior to re-injection. Solidification of LAVA may occur at the microcatheter tip resulting in microcatheter occlusion and use of excessive pressure to clear the microcatheter may result in microcatheter rupture.
- STOP injection if LAVA is not visualized exiting microcatheter tip. If the microcatheter becomes occluded, over-pressurization can occur. During LAVA injection, continuously verify that LAVA is exiting the microcatheter tip.
- STOP injection if increased resistance to LAVA injection is observed. If increased resistance occurs, determine the cause (e.g., LAVA occlusion in microcatheter lumen) and replace the microcatheter. Do not attempt to clear or overcome resistance by applying increased injection pressure, as use of excessive pressure may result in microcatheter rupture and embolization of unintended areas.
- Wait a few seconds following completion of LAVA injection before attempting microcatheter retrieval. Failure to wait a few seconds to retrieve the microcatheter after LAVA injection may result in fragmentation of LAVA into non-target vessels and embolization of unintended areas.

MRI SAFETY INFORMATION

- LAVA LES is MR Conditional for scanning in systems of 7 Tesla or less.

PRECAUTIONS

- The safety and effectiveness have not been studied in the following patient populations:
  - Nursing women.
  - Individuals less than 18 years old.
- Data indicates that DMSO potentiates other concomitantly administered medications.
- A garlic-like taste may be noted by the patient with use of the LAVA LES due to the DMSO component. This taste may last several hours. An odor on the breath and skin may be present.
- Inspect product packaging prior to use. Do not use if the sterile barrier is open or damaged.
- Use prior to expiration date.
- Verify that the microcatheters and accessories used in direct contact with LAVA are clean and compatible with DMSO.
- DMSO may interact with other embolic agents (e.g., coils). LAVA LES has been tested for compatibility with bare metal (platinum) embolic coils and Cook Medical Nester® Embolization Coils.
- Safety of LAVA at injected volumes greater than 3.5 mL into the patient has not been evaluated. Total volume of LAVA injected should not exceed 3.5 mL.

Difficult removal of microcatheter entrapment may be caused by any of the following:

- Angioarchitecture
- Vasospasm
- Reflux of the embolic agent
- Injection time

To reduce the risk of microcatheter entrapment, carefully select microcatheter placement and manage reflux of LAVA to minimize the factors listed above.

Should microcatheter removal become difficult, the following will assist in microcatheter retrieval:

- Carefully pull the microcatheter to assess any resistance to removal.
- If resistance is felt, remove any “slack” in the microcatheter.
- Gently apply traction to the microcatheter (approximately 3-4 cm of stretch to the microcatheter).
- Hold this traction for a few seconds and release. Assess traction on vasculature to minimize risk of hemorrhage.
- This process can be repeated intermittently until the microcatheter is retrieved.

Alternate technique for difficult to remove microcatheters:

- Remove all slack from the microcatheter by putting a few centimeters of traction on the microcatheter to create a slight tension in the microcatheter.
- Firmly hold the microcatheter and then pull it using a quick wrist snap motion 10-15 centimeters to remove the microcatheter from the LAVA cast.

Note: Do not apply more than 20 cm of traction to the microcatheter, to minimize risk of microcatheter separation.

For entrapped microcatheters:

- Under some difficult clinical situations, it may be safer to leave the microcatheter in the vascular system.
- This is accomplished by stretching the microcatheter and cutting the shaft near the entry point of vascular access allowing the microcatheter to remain in the artery.
- If the microcatheter breaks during removal, distal migration or coiling of the microcatheter may occur. Same day surgical resection should be considered to minimize the risk of thrombosis.

TRAINING

LAVA implantation should only be performed by physicians who have successfully completed training in the use of the product. Serious, including fatal, consequences could result with the use of LAVA without adequate training. Contact Sirtex Medical for information on training, contact information is listed at the end of this document.

CLINICAL STUDY RESULTS

Study Purpose and Objective

A clinical study was performed to establish a reasonable assurance of safety and effectiveness of the LAVA LES for embolization of arterial hemorrhage in the peripheral vasculature. A summary of the clinical study is presented below. The objective of this study was to evaluate the safety and effectiveness of LAVA LES embolotherapy for the treatment of hemorrhage from peripheral arteries.

Study Design

The Liquid Embolization of Arterial Hemorrhages in the Peripheral Vasculature Study or LAVA Study was a multicenter, prospective, single-arm trial of the LAVA LES in patients with peripheral arterial bleeding in need of treatment. Subjects were followed for 30 days post procedure. The study included 113 patients at 19 investigational sites.

Safety was 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 is compared to the rates reported in the literature after treatment with other modalities currently used to treat peripheral artery hemorrhage.

The study was powered for the primary effectiveness endpoint of Clinical Success as defined 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. 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%, the required sample size to achieve a level of 80% power was 101 Target Lesions. Assuming a 10% attrition rate through 30 days, a total of 113 subjects were needed to be enrolled. For the primary safety endpoint, success was determined if the lower limit of one-sided 97.5% confidence interval was greater than 82%.

A core laboratory was used for independent central assessment of angiographic endpoints. The study also utilized a Data Safety Monitoring Board (DSMB) and an independent Clinical Events Committee (CEC) for adjudication of clinical events and clinical endpoints in the study.

Clinical Inclusion and Exclusion Criteria

Enrollment in the LAVA Study was limited to patients who met the following inclusion criteria:

- Age ≥ 18 years
- Active arterial bleeding in the peripheral vasculature, documented on a suitable imaging study
- Subject or subject's legally authorized representative is able and authorized to provide written informed consent for the procedure and the study
- Subject is willing and able to comply with the specified follow-up evaluation schedule
- Life expectancy >30 days
- No prior embolization in the target territory.

Patients were not permitted to enroll in the LAVA Study if they met any of the following exclusion criteria:

- 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;
- Coexisting signs of peritonitis or other active infection;
- 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;
- Uncorrectable coagulopathies such as thrombocytopenia <40,000/μL, international normalization ratio (INR) >2.0;
- Contraindication to angiography or catheterization, including untreatable allergy to iodinated contrast media;
- 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;
- Known allergy or other contraindication to any components of LAVA LES including dimethyl sulfoxide (DMSO);
- More than 4 Target Lesions will require embolization, in the Investigator's opinion after performance of diagnostic angiography or another suitable imaging study.

Follow-up Schedule

All enrolled subjects were evaluated at hospital discharge and followed to 30 days after the index procedure. A schedule of assessments is provided in **Table 1** below:

Table 1. 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 eligibility 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 could have been performed via telephone with a member of the investigational site's research staff or with an in- person visit with the Investigator.

† Physical examination included vital signs and an examination of the target territory (as appropriate, e.g., the subject's limb) pre-procedure. Physical examination also included 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 prompted a duplex ultrasound or another appropriate imaging study to exclude false aneurysm, hematoma, arteriovenous fistula, dissection, or deep venous thrombosis.

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

§ The following laboratory tests were 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.

Clinical Endpoints

The primary safety endpoint was:

- Freedom from 30-day Major Adverse Events (MAEs) after enrollment, which include the following events as adjudicated by an independent CEC:
    1. Ischemia or infarction of the target territory.
    2. Non-target embolization: The target territory or territories were specified by the Investigator at the time of enrollment; embolization to a non-target territory was defined as unintentional administration of LAVA to a vascular bed outside of a target territory.
    3. Allergic reactions to LAVA.
    4. 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 did not trigger the endpoint.
    5. 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 of whether additional endovascular or open surgical procedures were performed.

The primary effectiveness endpoint was:

- Clinical success and is 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.

The study was considered a success if both the primary effectiveness and primary safety hypotheses were met.

Accountability of PMA Cohort

113 subjects were enrolled (successful arterial access established to the Target Lesion) at 19 sites. **Table 2** presents subject follow-up compliance. A total of 103 subjects were eligible at the 30-day follow-up visit and 10 were not eligible due to 9 who died prior to the 30-day visit and 1 who withdrew consent on post-procedure day 32.

Table 2. Subject Follow-up Compliance

Subject Compliance Characteristics	LAVA LES (N=113 Subjects)
Subjects at 30-Days	
Eligible Subjects[a]	103
Not Eligible Subjects	10
Reason not Eligible	
Not Past Due	0
Withdrew Consent	1
Investigator Withdrew Subject	0
Lost to Follow-up	0
Death	9
Other	0
Follow-up Not Done in Eligible Subjects	0
Follow-up visit within window[b]	86
Follow-up visit out of window[b]	17
Follow-up Compliance (%)c	84

[a] Eligible subjects are all subjects who are enrolled by snapshot date and either complete the study, have a follow-up visit form or are past due for their follow-up (beyond upper limit of window on study and did not exit the study before the upper limit of the window)

[b] Within window visits are defined as: 30 days ± 7 days;

[c] Percentage based on number of subjects who had follow-up visit within window divided by total number of eligible subjects

Site reported data.

All 113 patients were considered as part of the Intention-to-Treat (ITT) and Completed Cases (CC) Populations. The ITT population includes all consented subjects in whom the LAVA LES study device entered the vasculature, irrespective of adherence with the entry criteria, treatment received, subsequent withdrawal, or deviation from the Protocol. The CC population includes all ITT subjects who completed 30-day follow-up. The CC population also includes ITT subjects who experienced failure of the primary effectiveness endpoint prior to the beginning of the 30-day follow-up timepoint, irrespective of their length of follow-up.

Study Population Demographics and Baseline Parameters

Table 3 presents baseline demographics and medical history of the study population. Subjects were more frequently male (72; 63.7%), with a mean age of 57.4 years (range 18-93), average BMI of 28.9 kg/m^2 ± 6.88 and had comorbidities including hypertension (66; 58.4%), hyperlipidemia (36; 31.9%), renal insufficiency (32; 28.3%) and diabetes (28; 24.8%). Sixteen subjects (14.2%) had prior surgery at the target lesion.

Table 3. Baseline Demographic and Medical History

Subject Characteristics	LAVA LES (N=113 Subjects)
Age (Years)	
N	113
Mean ± SD	57.4 ± 18.00
Sex	
Female	36.3% (41/113)
Male	63.7% (72/113)
Ethnicity Hispanic or Latino	19.2% (20/104)
Race	
Asian	9.3% (10/108)
Black or African American	14.8% (16/108)
Native Hawaiian or other Pacific Islander	0.9% (1/108)
White	58.3% (63/108)
Other	16.7% (18/108
BMI (kg/m^2)	
N	113
Mean ± SD	28.9 ± 6.88
History of Diabetes	24.8% (28/113)
Prior Myocardial Infarction	7.1% (8/113)
Cardiac Valve Disorder	8.0% (9/113)
Hypertension	58.4% (66/113)
Coronary Artery Disease	18.6% (21/113)
Congestive Heart Failure	12.4% (14/113)
Chronic Obstructive Pulmonary Disease	8.0% (9/113)
Atrial Arrythmia	15.9% (18/113)
Ventricular Arrythmia	2.7% (3/113)
Collagen Vascular Disease	0.9% (1/113)
Aortic Aneurysm	1.8% (2/113)
Hyperlipidemia	31.9% (36/113)
Deep Venous Thrombosis	8.0% (9/113)
Pulmonary Embolism	6.2% (7/113)
Neurological Disorder	15.9% (18/113)
Cerebrovascular Disease	2.7% (3/113)
Stroke or TIA	6.2% (7/113)
Renal Insufficiency	28.3% (32/113)
Prior Surgery at Target Lesion	14.2% (16/113)
Bleeding Disorder	5.3% (6/113)
Peripheral vascular disease	7.1% (8/113)
Current Smoker	19.5% (22/113)

Numbers are % (counts/sample size) unless otherwise stated.

Table 4 summarizes baseline clinical characteristics. The most frequently encountered bleeding territories in the 113 subjects were gastrointestinal in 21 subjects (18.6%) and visceral (non-intestinal) in 41 subjects (36.3%). Among the subjects with visceral bleeding, the most common organs were the spleen (14, 34.1%) and the liver (12; 29.3%). The two most common etiologies were traumatic, non-iatrogenic (32; 28.3%) and iatrogenic (29; 25.7%).

Table 4. Baseline Clinical Characteristics

Subject Bleed Characteristics	LAVA LES (N=113 Subjects)
Target Bleed Territory	
Upper GI	9.7% (11/113)
Lower GI	8.8% (10/113)
Non-GI Visceral	36.3% (41/113)
Extremity	7.1% (8/113)
Pulmonary	0.0% (0/113)
Other	38.1% (43/113)
Upper GI Subset (N=11)	
Esophageal	0.0% (0/11)
Gastric	54.5% (6/11)
Duodenal	45.5% (5/11)
Lower GI Subset (N=10)	
Small Intestine	30.0% (3/10)
Colon	70.0% (7/10)
Rectal	0.0% (0/10)
Non-GI Subset (N=41)	
Splenic	34.1% (14/41)
Hepatic	29.3% (12/41)
Adrenal	2.4% (1/41)
Pancreas	7.3% (3/41)
Prostate	0.0% (0/41)
Bladder	0.0% (0/41)
Uterus	2.4% (1/41)
Other	24.4% (10/41)
Extremity Territory	
Right Arm	0.0% (0/8)
Left Arm	12.5% (1/8)
Right Leg	12.5% (1/8)
Left Leg	75.0% (6/8)
Etiology of Bleeding	
Traumatic, non-iatrogenic	28.3% (32/113)
Iatrogenic	25.7% (29/113)
Ulcer	4.4% (5/113)
Benign Neoplasm	0.9% (1/113)
Malignant Neoplasm	4.4% (5/113)
Mallory Weiss Tear	0.0% (0/113)
Congenital Vascular Lesion	0.0% (0/113)
Unknown	5.3% (6/113)
Other	31.0% (35/113)
Currently Taking Antiplatelet Agents	9.4% (9/96)
Currently Taking Anticoagulant Agents	8.9% (8/90)

Numbers are % (counts/sample size) unless otherwise stated.

Safety and Effectiveness Results

Safety Results

The analysis of the primary safety endpoint was based on the 101 subjects available for the 30-day follow-up period. All subjects (100%; 101/101) had Freedom from MAE at 30 Days. The primary safety endpoint was met with the lower limit of the one-sided 97.5% confidence interval being 96.4%, which was greater than the 82% performance goal.

As shown in **Table 5**, no subjects experienced major adverse events through 30 days based on data adjudicated by an independent CEC. The details of the Secondary Safety Endpoints at 30 Days are as follows:

- No subjects presented with symptomatic ischemia in the target territory that did not require intervention.
- All-cause mortality rate was 8.3% (9/109) through the 30-day follow-up timepoint. The denominator for the all-cause mortality rate excluded 4 subjects that exited the study before the 30-day follow-up visit without death. Of the 9 deaths, 8 were CEC adjudicated as being related to the procedure (since they occurred within 30 days of the index procedure) and 2 subjects as related to the device.
- Bleeding-related mortality that was attributable to the target territory was 1.9% (2/103).
- No subjects (0%; 0/101) required open surgical conversion for persistent or recurrent bleeding.
- Device-related Serious Adverse Events occurred in 4.9% (5/103) of subjects.
- Procedure-related Serious Adverse Event occurred in 23.1% (25/108) of subjects.
- No subjects (0%; 0/101) had access site hematoma >5cm in longest axis based on core-laboratory determined assessment of bleeding.
- No subjects (0%; 0/101) developed access site false aneurysm.

Table 5. Major Adverse Events and Secondary Safety Endpoints at 30 Days

Complications	LAVA LES (N=113 Subjects)
Major Adverse Events Composite	0.0% (0/101)
Non-target Embolization	0.0% (0/101)
Ischemia or Infarction of the Target Territory	0.0% (0/101)
Allergic Reactions to LAVA	0.0% (0/101)
Catheter Breakage	0.0% (0/101)
Catheter Entrapment	0.0% (0/101)
Secondary Safety Endpoints at 30 Days	
Symptomatic in the Target Territory not Requiring Intervention	0.0% (0/101)
All-cause Mortality	8.3% (9/109)
Bleeding-related Mortality	1.9% (2/103)
Open Surgical Conversion[a]	0.0% (0/101)
Device-related Serious Adverse Events	4.9% (5/103)
Procedure-related Serious Adverse Events	23.1% (25/108)
Access Site Hematoma (>5cm in longest axis)[b]	0.0% (0/101)
Access Site False Aneurysm[b]	0.0% (0/101)

Endpoint Definitions:

The Major Adverse Event (MAE) endpoint is defined as a composite safety endpoint, triggered by any of the following through 30 days following the index procedure:

- *Ischemia or Infarction of the Target Territory.*
- *Non-target Embolization defined as unintentional administration of LAVA to a vascul.ar bed outside of a target territory.*
- *Allergic Reactions to LAVA.*
- *Catheter Breakage defined as defects in the luminal continuity of the microcatheter used to deliver LAVA.*
- *Catheter Entrapment defined as the inability to withdraw the LAVA administration catheter requiring the need for endovascular or open surgical procedures to remove the catheter or portions thereof.*

Denominators are number of subjects who had the event before 23 days or had last contact date after 23 days.

[a]Site reported data.

[b]Core Lab reported data.

Other endpoints were CEC adjudicated.

Serious adverse events (SAE) by System-Organ Class (SOC) are summarized in **Table 6.** A total of 50 SAEs occurred in 35.4% (40/113) of subjects with 4.9% (5/103) that were device-related and 23.1% (25/108) that were procedure-related. The most frequent SAEs were vascular disorders (9.7%; 11/113), gastrointestinal disorders (5.3%; 6/113), blood and lymphatic system disorders (4.4%; 5/113) and general disorders and administration site conditions (4.4%; 5/113).

Table 6. Number of Subjects with One or More Serious Adverse Events by MedDRA System-Organ Class and Preferred Term

Adverse Event	LAVA LES (N=113 Subjects)
Subjects with one or more SAE	35.4% (40/113)
Blood and lymphatic system disorders[a]	4.4% (5/113)
Anemia	2.7% (3/113)
Chronic myeloid leukemia	0.9% (1/113)
Thrombocytopenia	0.9% (1/113)
Cardiac disorders[a]	3.5% (44/113)
Atrial fibrillation	1.8% (2/113)
Cardiac arrest	0.9% (1/113)
Chest pain	0.9% (1/113)
Gastrointestinal disorders[a]	5.3% (6/113)
Abdominal pain	1.8% (2/113)
Hematochezia	0.9% (1/113)
Ileus	0.9% (1/113)
Melaena	1.8% (2/113)
Small intestinal perforation	0.9% (1/113)
General disorders and administration site conditions[a]	4.4% (5/113)
Death	2.7% (3/113)
Flank pain	1.8% (2/113)
Hepatobiliary disorders[a]	1.8% (2/113)
Cholangitis infective	0.9% (1/113)
Gallbladder rupture	0.9% (1/113)
Infections and infestations[a]	3.5% (4/113)
Sepsis	3.5% (4/113)
Injury, poisoning and procedural complications[a]	1.8% (2/113)
Vascular pseudoaneurysm	1.8% (2/113)
Metabolism and nutrition disorders[a]	1.8% (2/113)
Acute respiratory failure	0.9% (1/113)
Respiratory failure	0.9% (1/113)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)[a]	1.8% (2/113)
Adenocarcinoma	0.9% (1/113)
Endometrial cancer	0.9% (1/113)
Renal and urinary disorders[a]	1.8% (2/113)
Acute kidney injury	0.9% (1/113)
Nephrolithiasis	0.9% (1/113)
Respiratory, thoracic, and mediastinal disorders[a]	1.8% (2/113)
COVID-19	0.9% (1/113)
Pleural effusion	0.9% (1/113)
Surgical and medical procedures[a]	0.9% (1/113)
Colectomy	0.9% (1/113)
Vascular disorders[a]	9.7% (11/113)
Cardiogenic shock	0.9% (1/113)
Epistaxis	0.9% (1/113)
Extravasation blood	2.7% (3/113)
Hematoma infection	0.9% (1/113)
Hepatic hemorrhage	0.9% (1/113)
Hypotension	0.9% (1/113)
Pulmonary embolism	0.9% (1/113)
Retroperitoneal hematoma	0.9% (1/113)
Septic shock	0.9% (1/113)
Shock hemorrhagic	0.9% (1/113)

[a]Event verbatim terms are reported by sites. The events listed in this table are then coded using MedDRA version 24 and then stratified by System-Organ Class (SOC) and Preferred Term. Patients may be counted in this table more than once by Preferred Term but are only counted once in each SOC summary line.

Numbers are % (counts/sample size) unless otherwise stated. Site reported and MedDRA coded data.

Effectiveness Results

The analysis of effectiveness was based on 113 evaluable patients and 148 lesions at 30 days. The primary effectiveness endpoint (Clinical Success at 30 Days) was achieved in 94.3% (133/141) of lesions **(Table 7).** The primary effectiveness endpoint was met with the lower limit of the one-sided 97.5% confidence interval bound of 89.1%, which was greater than the 72% performance goal. There were 8 lesions that had a bleed from the Target Lesion within 30 days. No subjects required emergency surgery or re-embolization. There were 2 lesions that required target lesion reintervention through 30-day follow-up.

Table 7. Clinical Success at 30 Days

Parameter	LAVA LES (N=113 Subjects, n=148 Lesions)
Clinical Success at 30 Days	94.3% (133/141)
Absence of Bleeding from Target Lesion	94.3% (133/141)
No Emergency Surgery	100% (141/141)
No Re-embolization	100% (141/141)
No Target Lesion Reintervention	98.6% (139/141)

Endpoint Definitions:

Clinical Success is defined as:

- *Absence of bleeding from the target lesion defined as no BARC Type 3 or greater bleeding, either persistent or recurrent 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.*

Numbers are % (counts/sample size) unless otherwise stated.

Site/Core Laboratory reported and Clinical Events Committee adjudicated data.

The secondary effectiveness endpoints of: (1) technical success, defined as absence of angiographic evidence of bleeding from target lesion at the conclusion of the index procedure was 97.3% (144/148) of lesions and (2) successful delivery of LAVA and intact retrieval of the microcatheter was achieved in all 141 (100%) evaluable lesions.

Subgroup Analyses

A subgroup analyses was conducted based on gender **(Table 8).** Males accounted for 72 subjects and 95 lesions compared to 41 female subjects and 53 lesions. Clinical Success at 30 Days was significant between the genders with greater clinical success in the male population. Freedom from MAE at 30 Days was the same at 100% in both populations. Other notable differences were all-cause mortality rate being higher in females (M: 5.8%; 4, F: 12.5%; 5) and both Device and Procedure related SAEs being higher in the female population (Device – M: 3.1%, F: 7.9%, Procedure – M: 17.4%, F: 33.3%). All other characteristics were similar including Technical Success and Successful Delivery of LAVA.

Table 8. Primary and Secondary Endpoint Analysis - Male and Female

Male Female Parameter	Male (N=72 Subjects, n=53 Lesions)	Female (N=41 Subjects, n=95 Lesions)
Primary Effectiveness Endpoint		
Clinical Success at 30 Days	98.9% (89/90)	86.3% (44/51)
P-value*	0.003	
Primary Safety Endpoint		
Freedom from MAE at 30 Days	100% (65/65)	100% (36/36)
Secondary Effectiveness Endpoints		
Technical Success	96.8% (92/95)	98.1% (52/53)
Successful Delivery of LAVA and Intact Retrieval of the Microcatheter	100% (92/92)	100% (49/49)
Secondary Safety Endpoints		
Major Adverse Events Composite at 30 Days	0.0% (0/65)	0.0% (0/36)
Non-target Embolization	0.0% (0/65)	0.0% (0/36)
Ischemia or Infarction of the Target Territory	0.0% (0/65)	0.0% (0/36)
Allergic Reactions to LAVA	0.0% (0/65)	0.0% (0/36)
Catheter Breakage	0.0% (0/65)	0.0% (0/36)
Catheter Entrapment	0.0% (0/65)	0.0% (0/36)
Symptomatic Ischemia in the Target Territory not Requiring Intervention at 30 Days	0.0% (0/65)	0.0% (0/36)
All-cause Mortality at 30 Days	5.8% (4/69)	12.5% (5/40)
Bleeding-related Mortality at 30 Days	0.0% (0/65)	5.3% (2/38)
Open Surgical Conversion at 30 Days	0.0% (0/65)	0.0% (0/36)
Device-related Serious Adverse Events at 30 Days	3.1% (2/65)	7.9% (3/38)
Procedure-related Serious Adverse Events at 30 Days	17.4% (12/69)	33.3% (13/39)
Access Site Hematoma (>5cm in longest axis) at 30 Days	0.0% (0/65)	0.0% (0/36)
Access Site False Aneurysm at 30 Days	0.0% (0/65)	0.0% (0/36)

**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.*

Clinical Study Conclusions

In conclusion, the study met the study success criteria in both the primary effectiveness and primary safety hypotheses. Effectiveness of the device was demonstrated in terms of clinical success, technical success, and successful device delivery. The LAVA LES has confirmed a favorable safety profile in terms of freedom from MAEs, symptomatic ischemia in the target territory not requiring intervention, access site hematomas and access site false aneurysms. The results of the study confirm the safety and effectiveness of the LAVA LES device when used for the embolization of arterial hemorrhage in the peripheral vasculature.

STORAGE

Store the LAVA LES at ambient temperature. Prior to use, maintain product temperature between 19° and 24°C. If product solidifies due to exposure to colder temperatures, thaw at room temperature before use.

LAVA MIXING AND PREPARATION

LAVA can be mixed using the LAVA Mixing Kit per the directions for use below.

Alternatively, the LAVA vial can be mixed for 20 minutes at a setting of 3000 RPM on the suggested vortex mixer (Scientific Industries SI-A236) or the equivalent setting on an analog vortex mixer to fully mix the suspension. The vortex mixer will require Scientific Industries vial adapter SI-V203 for the 6 mL product and Scientific Industries vial adapter SI-0570 for the 2 mL product.

1. Select the LAVA Mixing Kit that is compatible with the specific LAVA LES Kit to be used in the procedure per the chart below:

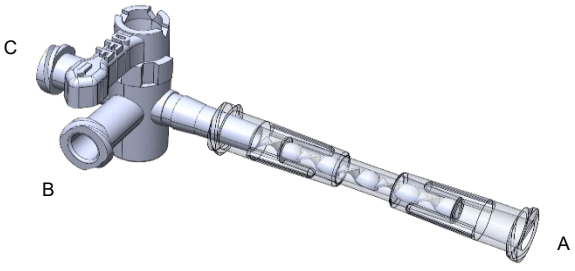
LAVA LES Kit		LAVA Mixing Kit	
Product	**SKU**	**Product**	**SKU**
LAVA-18, 2 mL	SLLES182	LAVA Mixing Kit - 2 mL	SLLESMK2
LAVA-18, 6 mL	SLLES186	LAVA Mixing Kit - 6 mL	SLLESMK6
LAVA-34, 2 mL	SLLES342	LAVA Mixing Kit - 2 mL	SLLESMK2
LAVA-34, 6 mL	SLLES346	LAVA Mixing Kit - 6 mL	SLLESMK6

2. Remove the contents of the LAVA Mixing Kit using sterile technique and place on the sterile field.
3. Mix the LAVA vial for at least 1 minute at a setting of 3000 RPM on the suggested vortex mixer and accessories (Scientific Industries SI-A236, SI-0511, SI-0570) or the equivalent setting on an analog vortex mixer. LAVA should be solid black in color after mixing.
4. Withdraw all of the premixed LAVA in the vial into the mixing syringe included in the LAVA Mixing Kit via an 18G or larger needle.
5. Detach the mixing syringe from the needle. Attach the mixing syringe to luer port “A” of the mixing manifold included in the LAVA Mixing Kit as shown in the illustration below.
6. Turn the flow diverter “Off” arrow of the mixing manifold towards luer port “C” of the mixing manifold then prime the mixing manifold by filling the fluid path (up to luer port “B” of the mixing manifold) with premixed LAVA.
7. Attach the second mixing syringe included in the LAVA Mixing Kit to luer port “B” of the mixing manifold and perform syringe-to-syringe mixing for at least 16 passes immediately prior to delivery. One pass comprises transferring the contents of one mixing syringe through the mixing manifold and into the opposite mixing syringe.

> **WARNING**
>
> Failure to perform syringe-to-syringe mixing for at least 16 passes may result in inadequate suspension of the tantalum, resulting in inadequate fluoroscopic visualization during delivery.

8. Return the mixed LAVA to the mixing syringe attached to luer port “A”.
9. Remove a 1 mL delivery syringe (denoted by the white plunger) from the LAVA LES Kit and fully depress the syringe piston until the plunger is bottomed out.
10. Attach the 1 mL delivery syringe to luer port “C” and then turn the flow diverter “Off” arrow towards luer port “B”.
11. Fill the delivery syringe with 1 mL of mixed LAVA by slowly depressing the mixing syringe plunger. Before disconnecting the delivery syringe from the mixing manifold, verify that LAVA is free of air bubbles.
12. Turn the flow diverter “Off” arrow towards luer port “C” and then disconnect the delivery syringe from the mixing manifold.
13. Follow the LAVA LES **“DIRECTIONS FOR USE”** below on how to deliver LAVA to the patient.

In the event that the LAVA needs to be remixed, or additional LAVA is required for the procedure, perform syringe-to-syringe mixing for at least 16 passes immediately prior to delivery per step 7, then fill another 1mL delivery syringe provided in the LAVA LES Kit per the **“LAVA MIXING AND PREPARATION”** instructions above.



DIRECTIONS FOR USE

1. Confirm microcatheter placement with injection of contrast agent per institutional procedure.
2. Flush contrast from microcatheter with 10 mL of saline. Leave the syringe connected.
3. Ensure that LAVA has been mixed per the **“LAVA MIXING AND PREPARATION”** instructions above.
4. Withdraw approximately 0.8 mL of DMSO from the LAVA LES Kit into the 1 mL DMSO syringe (denoted by the yellow plunger). Inject DMSO into the delivery microcatheter in sufficient volume to fill the microcatheter dead space. Refer to the delivery microcatheter manufacturer’s labeling for dead space volume.
5. As soon as the DMSO has been injected into the microcatheter dead space, remove the 1 mL DMSO syringe, hold the microcatheter hub in a vertical position, and overfill and wash the luer hub with the balance of the DMSO.
6. Connect the 1 mL delivery syringe to the hub making sure there is no air in the hub during the connection, and immediately re-position the 1 mL delivery syringe horizontally.
7. Begin injecting LAVA to displace the DMSO. It is recommended that LAVA be injected at a slow, steady rate not to exceed 0.3 mL/min.

> **WARNING**
>
> - Failure to properly mix LAVA may result in inadequate suspension of the tantalum, resulting in inadequate fluoroscopic visualization during delivery.
> - Inject LAVA immediately after mixing. If injection of the mixed LAVA is delayed, tantalum settling can occur within the syringe resulting in poor visualization of LAVA during injection.
> - Use only thumb pressure to inject LAVA. Do not use the palm of the hand to advance plunger during injection of LAVA as that may result in microcatheter rupture due to over pressurization in the event of microcatheter occlusion.
> - STOP injection if increased resistance to LAVA injection is observed. Do not attempt to clear or overcome resistance by applying increased injection pressure, as use of excessive pressure may result in microcatheter rupture and embolization of unintended areas.
> - DO NOT interrupt LAVA injection for longer than two minutes prior to re- injection. Solidification of LAVA may occur at the microcatheter tip resulting in microcatheter occlusion, and use of excessive pressure to clear the microcatheter may result in microcatheter rupture.
> - Adequate fluoroscopic visualization must be maintained during LAVA delivery or non-target vessel embolization may result. If visualization is lost at any time during the embolization procedure, halt LAVA delivery until adequate visualization is re-established.

8. Monitor volume injected to correspond to volume of vascular space being filled. Total volume of LAVA injected should not exceed 3.5 mL.
9. Upon completion of the injection of LAVA, wait a few seconds, slightly aspirate the syringe, and then gently pull the microcatheter to separate it from the LAVA cast.

Should microcatheter removal become difficult, the following will assist in microcatheter retrieval:

- Carefully pull the microcatheter to assess any resistance to removal.
- If resistance is felt, remove any “slack” in the microcatheter.
- Gently apply traction to the microcatheter (approximately 3-4 cm of stretch to the microcatheter).
- Hold this traction for a few seconds and release. Assess traction on vasculature to minimize risk of hemorrhage.
- This process can be repeated immediately until microcatheter is retrieved.

Optional microcatheter retrieval technique:

- Remove all slack from the microcatheter by putting a few centimeters of traction on the microcatheter to create a slight tension in the microcatheter.
- Firmly hold the microcatheter and then pull it using a quick wrist snap motion 10 – 15 centimeters to remove the microcatheter from the LAVA cast.

Note: Do not apply more than 20 cm of traction to microcatheter, to minimize risk of microcatheter separation.

For information on training, please contact Sirtex Medical Inc. at csusa@sirtex.com or 888-474-7839.

SYMBOL GLOSSARY			
STERILE EO	Syringes are sterile (sterilized using ethylene oxide)		Keep away from sunlight
STERILE	LAVA and DMSO are sterile (sterilized using dry heat)		Keep dry
STERILE R	Mixing manifold is sterile (sterilized using electron beam)		Do not use if package is damaged
	Single use	REF	Reference number
Rx ONLY	Caution: Federal (USA) law restricts this device to sale by or on the order of a physician	LOT	Lot number
STERILIZE	Do not resterilize	CONTENTS	Contents of package
	Caution: consult instructions for use		Use by
	Non-pyrogenic		Manufacturer
MR	LAVA LES is MR Conditional for scanning in systems of 7 Tesla or less		