Study Name

The LAVA Study

Study Number

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Study Title

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

Clinical Investigation Plan

DCO#: 00618

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BlackSwan VASCULAR

Liquid Embolization of Arterial Hemorrhages in

Peripheral Vasculature

The LAVA Study

Statistical Analysis Plan

[redacted]

APPROVALS

[redacted]

Approval indicates review and agreement with the document as written

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Liquid Embolization of Arterial Hemorrhages in the Peripheral Vasculature
The LAVA Study

Study Description: This statistical analysis plan (SAP) is for a prospective, multicenter, single-arm study of the Lava™ Liquid Embolic System (LES) for the embolic treatment of arterial hemorrhage in the peripheral vasculature compared to performance goals.

Objectives: To evaluate the safety and effectiveness of the Lava LES for the embolic treatment of arterial hemorrhage in the peripheral vasculature. The study will test the proportion of Target Lesions with 30-day Clinical Success against a 72% performance goal and test the proportion of subjects experiencing freedom from 30-day major adverse events against a 82% performance goal both tests using a one-sided exact confidence interval and one-sided alpha level of 0.025.

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.

Study Population: The study will enroll 113 male and female US subjects at least 18 years of age 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.

Phase: This is a pivotal Investigational Device Exemption (IDE) study.

Description of Study Treatment: 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. 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. 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.
Study Duration:	It is estimated that enrollment will take 12 months, subjects will be followed for 30 days and data analysis will take 3 months for a total of 16 months study duration.
Participant Duration:	The institutional Principal Investigator (PI), treating physician or experienced personnel should conduct a close follow-up with scheduled patient visits and examinations as needed.

2 ENDPOINT DEFINITIONS

The primary safety endpoint is a composite of freedom from 30-day 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 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.

The primary effectiveness endpoint[1] 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.[2] Effectiveness relates to the target lesion(s) as defined by the Investigator at the index procedure.

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 within 30 days of the index procedure;
4. Symptomatic ischemia in the target territory that does not require intervention within 30 days of the index procedure;
5. All-cause mortality within 30 days of the index procedure;
6. Bleeding-related mortality (attributable to bleeding in a target territory) within 30 days of the index procedure;
7. Open surgical conversion for persistent or recurrent bleeding within 30 days of the index procedure;
8. Device-related serious adverse events within 30 days of the index procedure;
9. Procedure-related serious adverse events within 30 days of the index procedure;

[1] 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.

[2] 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.

10. Access site hematoma (>5cm in longest axis) within 30 days of the index procedure;[3]
11. Access site false aneurysm within 30 days of the index procedure;
12. Units of red blood cells transfused after administration of Lava;
13. Duration of the index procedure, total and after administration of Lava;
14. Contrast administered the during index procedure;
15. Fluoroscopy time during the 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.

3 STATISTICAL CONSIDERATIONS

3.1 STATISTICAL HYPOTHESES

Success or failure of the study will be based on the primary effectiveness and safety endpoints, with descriptive assessment of the 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 of 72%.

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:

H_0: $Ps \leq PG_S$ versus

H_A: $Ps > PG_S$,

[3] As measured on a duplex ultrasound study, assessed by the Core Laboratory.

where Ps is the population primary safety success rate in the Test group and PG_S is the safety performance goal of 82%.

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 greater than 82%.

3.2 SAMPLE SIZE DETERMINATION

A literature search identified 67 publications reporting outcome for 2102 patients treated with embolotherapy for peripheral arterial hemorrhage.[4] 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.

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. 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 subjects 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 shown in **Table 1** below. Assuming that the safety success rate is 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%.

[4] 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).

Table 1. 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%

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. This rate was consistent with the expected outcomes reported in the Society of Interventional Radiology document. An 8% margin was used to assign the effectiveness performance goal of 72%.

The study is powered for the primary effectiveness endpoint of Clinical Success. Based upon a one-sided 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%,[5] 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.

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

Table 2. 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 3**, below.

Table 3. 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

3.3 POPULATIONS FOR ANALYSES

The intention to treat (ITT) dataset, defined as 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, 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 (see 3.4.1 handling of missing data).

The complete cases (CC) dataset, defined as all ITT subjects who complete 30-day follow-up, 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 (completed 30-day follow-up). 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.

3.4 STATISTICAL ANALYSES

3.4.1 GENERAL APPROACH

Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analysis will be conducted using {SAS version 9.4 or later (SAS Institute Inc., Cary, NC)} or other widely accepted statistical or graphical software as required.

Descriptive Statistics

Continuous data will be summarized with mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical variables will be summarized with frequency counts and percentages. Confidence intervals may be presented, where appropriate, using the t-distribution for continuous data and exact binomial method for categorical variables.

Study Visit

Study visit Day 0 is the date of the index procedure. Days in study will be calculated relative to the index procedure as follows:

Study Days = Assessment Date – Index Procedure Date

For each subject, duration in study will be based on last study contact date which is the latest date of all follow-up visits, assessments, adverse event onset or resolution, and study exit including date of death.

Duration variables will be calculated as follows:

Duration Days = End Date – Start Date

Visit Windows

Unless otherwise specified, visit assessments will be analyzed for each analysis time point according to the visit entered in the electronic Case Report Form (eCRF).

Statistical Significance

Unless otherwise specified, hypothesis testing will be performed at the two-sided 0.05 significance level. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001". If a p-value is greater than 0.999, it will be reported as ">0.999".

Reporting Precision

Unless otherwise specified, the following conventions will apply for data display. In general, percentages will be displayed to 1 decimal place. Percentages <0.05% will be reported to 2 decimal places. For continuous parameters, means and medians will be reported to 1 additional decimal place than the measured value while standard deviation will be reported to 2 additional decimal places than the measured value. Minimum and maximum values will be reported to the same precision as the measured value.

Handling of Missing Data

All attempts will be made to limit the amount of missing data. For all analyses of the primary endpoints, the number of observations available will be reported so the reader can assess the impact of missing data. In general, and for the primary endpoint analyses, missing data will not be imputed and analyses will be based on available data. For missing values on the primary safety endpoint, an adjustment to the denominator will be made based on the amount of evaluable data. For each visit (or reporting time point), the occurrence rate will be calculated as the number of subjects with certain endpoint occurrence term over the number of evaluable subjects. The evaluable subjects at each reporting time point include all subjects who are enrolled by the snapshot date and

1) had an endpoint occurrence within (on or before) the reporting cutoff days (30 days), or
2) had a follow-up at or after the lower limit of the reporting window (23 days), or
3) the withdrawal consent date/recorded lost-to-follow-up date at or after the lower limit of the reporting window.

Sensitivity analyses will be performed to assess the impact of missing data and potential correlation in the data for the primary endpoints. Three different sensitivity analysis are planned: (1) As described in the protocol, 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. (2) A tipping point analysis will be conducted in which lesions or subjects censored without an event prior to 30 days follow-up are sequentially imputed as failures at the time of censoring. (3) A generalized estimating equation (GEE) logistic regression model will be used to estimate clinical success taking into account potential correlation of multiple Target Lesions within a subject using an exchangeable working correlation structure. The analyses for all the secondary endpoints will not include imputation for missing data, and no formal statistical hypotheses will be tested.

More generally, in the case of partial adverse event onset date or date of death, the unknown portion of the date of the event will be imputed. If the month and year are known, the 1st of the month will be used for analysis. If only the year is known, the event will be analyzed as if it occurred on June 30th of the known year. In the rare case that the date is fully unknown, the date will be imputed as the initial treatment date. Imputation of partial dates is subject to the condition that it

must occur on or after the initial treatment date. In the case where the imputed date is prior to the initial treatment date, the date of the initial treatment will be used. As death cannot occur before any documented subject contact, for date of death the imputed date of death must occur on or after last known contact in study.

3.4.2 ANALYSIS OF THE PRIMARY ENDPOINT

Success or failure of the study will be based on the primary effectiveness and safety endpoints, with descriptive assessment of the 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 of 72%.

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:

H_0: $Ps \leq PG_S$ versus

H_A: $Ps > PG_S$,

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

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%. Handling of missing data is described in section 3.4.1.

3.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Binary endpoints will be analyzed with frequency counts and proportions. Exact binomial 95% confidence intervals will be used as descriptive measures. Time-to-event analyses may be employed as an additional descriptive analysis to account for partial follow-up, as applicable. Continuous endpoints will be summarized with mean, standard deviation, median, minimum, maximum, and number of

evaluable observations. Confidence intervals may be presented, where appropriate, using the t-distribution.

3.4.4 SAFETY ANALYSES

Adverse Events (AEs) will be coded by Medical Dictionary for Regulatory Activities (MedDRA)), calculated with each AE counted once only for a given participant and presented (severity, frequency, and relationship of AEs to study device and procedure) by System Organ Class (SOC) and preferred term groupings. The following information will be reported about each AE; start date, stop date, severity, relationship, expectedness, outcome, and duration.

Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented in a listing.

3.4.5 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics will be presented for clinically relevant baseline demographic, medical history, and clinical characteristic variables.

3.4.6 PLANNED INTERIM ANALYSES

The Data Safety Monitoring Board (DSMB) will review safety data (including components of the primary endpoint, since these may impact safety) regularly to ensure that it is ethical to continue the study, based on the absence of unacceptable risks to the study cohort. There will be no formal interim analyses of the primary endpoint, however, 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. The timing and frequency of safety monitoring will be described in the DSMB Charter.

3.4.7 SUB-GROUP ANALYSES

Subgroup analyses 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.

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.

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.

3.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and time point.

3.4.9 EXPLORATORY ANALYSES

There are no exploratory analyses planned for this study.

4 DATA HANDLING AND QUALITY ASSURANCE

4.1 DATA MANAGEMENT

Refer to the Data Management Plan (DMP).

4.2 QUALITY ASSURANCE

Refer to the Quality Assurance SOP for the quality assurance plan.

4.3 ACCESS TO RAW DATA AND ANALYSIS RESULTS

Refer the DMP for the database information. For the analysis results, access is limited to the programmers and the statistician until all patients have reached all the powered endpoints, the database is cleaned and ready for analysis and the primary endpoint analysis is complete.

5 ABBREVIATIONS

AE	Adverse Event
CC	Complete Cases
CMP	Clinical Monitoring Plan
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
IDE	Investigational Device Exemption
ITT	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
US	United States

6 REFERENCES

There are no references for this study.

7 APPENDICIES

There are no appendices for this study.